Cancer Research UK analysis of Clinical Trials Regulation  
September 2012

Summary
Cancer Research UK is broadly supportive of the draft Regulation adopted by the European Commission on 17 July 2012 and its aim to streamline and improve the regulatory environment in Europe. We believe that as a Regulation this legislation will achieve one of its principle goals in harmonising the regulatory system for clinical research across Europe.

Provisions in the new Regulation will improve the application and conduct of multinational trials. For example, we welcome the formalisation of the concept of co-sponsorship as well as the introduction of a single European portal for applications.

The main concerns for Cancer Research UK are about how the Regulation will work in practice. While provisions such as the single European application portal are welcomed, we need to understand how the new systems will operate.

Our analysis indicates that the Regulation may not produce significant steps in reducing the bureaucracy involved in running cancer studies. The proposed Regulation is not just an opportunity to streamline and enshrine current best practice; it also offers the opportunity to significantly improve aspects of setting up and running clinical trials. For example, we believe the Regulation could go further still in reducing the reporting requirements for staff and clinicians running the trials.

We are also concerned that the proposed introduction of low risk interventional trials in the Regulation does not provide a sufficient risk based approach. We believe that the European Commission and other institutions and organisations should explore ways to reduce the application and reporting requirements for clinical trials using marketed products with established safety profiles.

This analysis and resulting recommendations was informed by discussions with Cancer Research UK’s Clinical Trials Units and trial funding staff, the Cancer Research UK Drug Development Office and Cancer Research UK’s Chief Clinician.

Recommendations

1. We welcome the establishment of a single European portal as an important step to streamlining the application process for clinical trials but we need to have more detail on how it will operate in practice.

2. The Regulation should recognise that trials involving Investigational Medicinal Products (IMP) can still be considered low-interventional even if the medicine is being used outside of its existing indication.

3. Elements of the safety reporting system should be clarified and reconsidered in order to streamline reporting to benefit both patients and trialists.

4. We would like further revision to ensure more emphasis is placed on the sponsor to decide whether to report substantial modifications.

5. Co-sponsorship should be enshrined as it is set out in the Regulation.
6. We would welcome further clarity on how the Regulation relates to existing pieces of clinical trials legislation and guidance.

7. Further detail on the scope and flexibility of the national indemnity scheme needs to be outlined.

Background
The Clinical Trials Regulation is proposed to replace the Clinical Trials Directive (2001/20/EC), which governs how clinical research is regulated in the EU Member States. The Regulation seeks to address several criticisms of the original Directive from across industry, academia and patient groups.

It has been widely acknowledged that, since it was implemented, the Clinical Trials Directive (CTD) has contributed to the decline in the number of applications for clinical trials and increased costs and delays in setting up clinical trials. Figures from the European Commission suggest that between 2007 and 2011 the number of applications for clinical trials taking place in Europe fell by 25%.1 For non-commercial sponsors, such as Cancer Research UK’s clinical trials units, the Directive led to an average 98% increase in administrative costs and created delays in the set up of clinical trials.

Ensuring that the right regulatory environment exists to conduct clinical trials is crucial for patients and researchers in the UK. Without a proportionate regulatory environment, new treatments and methods would not be able to be tested to see if they are effective in treating cancer. Cancer Research UK has been working to secure an environment that both ensures the safety of patients who participate in clinical trials while also calling for a reduction in bureaucracy to allow our researchers to set up and run trials quickly.

In February 2012, Cancer Research UK released a report Supporting research, protecting patients: Cancer Research UK’s recommendations to reform the Clinical Trials Directive which highlighted the key problems with the Directive.2 Key issues that we wanted the new Regulation to address included harmonising regulations across member states; creating a risk based approach to clinical research; and limiting the amount of reporting that studies are required to undertake. For a full list of the recommendations please see Annex I.

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2 Cancer Research UK, Supporting research, protecting patients: Cancer Research UK’s recommendations to reform the Clinical Trials Directive, p.2
Single European portal
The Regulation sets out provisions for a single EU portal which would be used to apply for both multinational and national clinical trials. This would be a positive development as it could standardise the application process and provide a simplified mechanism for national trials to add additional sites in other Member States. The portal would help to remove discrepancies between Member States’ approvals, which would facilitate set up of multinational trials.

The text of the Regulation currently does not provide enough detail for the clinical trial community to understand how exactly it will operate in practice, and in order to fully support the proposal we are seeking further clarity from the Commission.

Member State approval process
The Regulation provides an option to select which Member State should lead on the assessment of a multinational trial. There could possibly be an issue if one Member State was consistently selected as the reporting Member State. If an agency such as the Medicine and Healthcare products Regulatory Agency was overburdened with multinational trials, it could possibly be to the detriment of the assessment of single country national trials.

The Regulation contains provisions for Member States to set their assessment fees as they wish. While price could be used to control demand to particular Member States we would be concerned that popular regulatory authorities would price themselves highly to control the number of multinational study applications they receive, which would in turn increase costs for single country trials.

Non-reporting member states are able to withdraw from a particular trial if they deem that its procedure falls outside the context of normal clinical practice. Normal clinical practice would continue to differ significantly across Member States and therefore there continues to be scope for Member States not to participate in multinational trials. This is particularly problematic for trials in rare cancers in which there is little or no evidence base on which to base a definition of normal practice. Sponsors should ideally be able to check what constitutes normal clinical practice in different Member States to help streamline the application process.

Cancer Research UK’s regulatory staff value the dialogue with the MHRA for single country trials, as this can currently be important when starting a study and preparing an application, and wish for this to be maintained.

The Regulation removes the definitions of a competent authority and ethics committee, leaving each member state to set up internal mechanisms of assessment of ethics. We are pleased that Member States will continue to have the ability to have their own ethics systems in place. A single approval will now be produced by Member States combining both regulatory and ethical

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3 Chapter II, Article 5, 1, p.28
4 Chapter II, Article 5, 2, p.29
5 Chapter XIV, Article 82, p.64
6 Chapter II, Article 2, 8, p.33
7 Introduction, p.5
approvals, this approval will be standardised across Member States. However we are concerned that reaching an agreement on a single application form for ethical approvals that is suitable for all Member States may be difficult.

**Study design**
The Regulation appears to contain provisions for Member States to assess the robustness of a clinical trial’s study design.\(^8\) This is a concern as the review of study design of academic cancer trials taking place in the UK is already conducted to a high standard by the funder/peer review body. Checking for robustness of design at the authorisation level could be unnecessarily duplicative and may undermine well established peer review/funding mechanisms in place within the UK.

**Data monitoring and recording**
Additional information will be required to be submitted to the EU database including trial time-points and results. The database needs to be easily accessible, user friendly and efficient to allow for this increase in usage.

Timelines for reporting the end of trial are significantly shorter than before. The Regulation requires 15 days while the current time line is 90 days for trials completing as per protocol.\(^9\) Again, depending on the efficiency of the system and the database, and the amount of data required, this could either be straightforward or a drain on resource. Timelines that are too ambitious may lead to a decrease in the quality of data available.

The Regulation makes requirements for reporting each time the first new patient is recruited in a Member State.\(^10\) As with other reporting issues in the Regulation, if the system is straightforward, this could be beneficial as it has the potential to monitor set up time of trials across member states.

Overall, there appears to be an emphasis throughout the Regulation on data monitoring and recording. These requirements currently exist with regulators and researchers applying them proportionality to the trial. The Regulation would put many of these requirements into legislation, which has the potential to create significant additional administrative burdens without proven gains in quality.

**Staff training**
The retraining of staff on new systems and procedures is a significant cost and administrative burden on trials units. The implementation and subsequent inspections of the Regulation by Member States should take this into account.

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\(^8\) Chapter II, Article 6, 1a, p.30
\(^9\) Chapter VI, Article 34, 1, p.48
\(^10\) Chapter VI, Article 37, 2, p.50
Recommendations

1. **We welcome the establishment of a single European portal as an important step to streamlining the application process for clinical trials but we need to have more detail on how it will operate in practice.**
   - There should be an option in place to ensure that Member States’ regulatory authorities can switch assessments of multinational trials to other countries if they are unable to cope with the workload.
   - Normal clinical practice should be clearly defined by each Member State to assist with running multinational trials.
   - Regulatory agencies in the UK should work towards making the portal compatible with existing regulatory approval systems in Member States.
   - Member States should continue to be the main contact for regulatory advice for applications.
   - Assessment of study design should take into account the level of peer review a study has already been subject to
   - The new system should be accessible to all staff involved in a trial and not prohibitively restricted to a number of individuals in an organisation

Risk-based approach

Cancer Research UK acknowledges and welcomes that the Regulation provides more clarity than the Directive regarding what constitutes a clinical trial and that it will not draw other clinical studies into the scope of the Regulation.

However, the Regulation still does not take into account how much existing information is already known about an intervention and the potential risk to patients and will therefore not achieve a truly risk-based approach to regulation.

Low interventional clinical trials

We understand that introduction of the concept of a low interventional trial appears to principally benefit pharmaceutical phase IV studies and would not reduce the amount of oversight and monitoring required for trials run by Cancer Research UK units including trials of licensed products.\(^\text{11}\)

As it stands, the Regulation will only consider trials low interventional (or low risk) if the IMP is used in the trial within its existing licence or its off licence use is standard practice. All other trials would be considered to pose the same level of risk, irrespective of the stage of development of the drug. For example, a trial using an IMP that had come off patent would be considered to have the same level of risk associated with a first in man study by the Regulation, if used in a new indication. Similarly, if a cancer treatment which was licensed for the adjuvant treatment of early disease only is trialled in the metastatic setting, it would not be considered a low risk trial according to the Regulation, despite the fact that the safety profile in that disease is well established. For the Regulation to be truly risk adapted it must take into consideration the established safety profile of a treatment.

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\(^{11}\) Chapter I, Article 2, 3, p.26
This is a specific problem in the paediatric settings in which there have historically been very few licences granted in such indications despite a considerable knowledge base as to the safety profile.

In the UK a ‘broad use’ term has sometimes been applied in the cancer setting. This has allowed for an authorised drug to be considered as being used within ‘broad use’ of the terms of its marketing authorisation if licensed for one tumour type (e.g. non-small cell lung cancer) but is being used within a trial in another tumour type (e.g. mesothelioma). This has been applied in particular in relation to IMP labelling ‘exemptions’. It would be useful to academic trials for the idea of ‘broad use’ to be enshrined in the Regulation, for example to extend the definition of ‘low-intervention clinical trial’.

**Definition of an Innovative Medicinal Product (IMP)**

The key definition that the Regulation has not changed is what product can be considered an IMP.\(^{12}\) We had previously called for a tighter and clearer definition of what products constitute an IMP and those that are ‘truly investigational’.\(^{13}\) Under the Regulation, reference products which are used to compare the efficacy or safety of the test treatment are still to be defined as an IMP even if their use is standard clinical practice. We believe that reference products in a trial should not be classified as IMPs if their use is standard clinical practice.

The Regulation has introduced the concept of an auxiliary medicinal product, which has replaced the definition of a Non-Investigational Medicinal Product (NIMP).\(^{14}\) Although there are subtle changes in the definition, the change in nomenclature adds a significant administrative burden in terms of updating quality documentation and procedures for little obvious gain.

**Labelling**

The Regulation appears to require additional information for labelling an IMP, we would want to ensure that labelling requirements are proportionate and supportive of patient safety. We welcome that the labelling requirements appear to be linked to the level of risk associated with the product and hope that this will reduce requirements on trialists.\(^{15}\)

**Recommendations**

2. **The Regulation should recognise that trials involving Investigational Medicinal Products (IMP) can still be considered low-interventional even if the medicine is being used outside of its existing indication.**
   - The Regulation should recognise that trials using licensed treatments, even when used outside the licensed indication, do not pose the same risk as trials of unlicensed treatments. This will be the key factor in reducing the regulatory burden for clinical trials.
   - Under the Regulation, many reference products will continue to be defined as IMPs although they are used in normal clinical practice.

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\(^{12}\) Chapter I, Article 2, 5, p.26  
\(^{13}\) Cancer Research UK, *Supporting research, protecting patients*, p.7  
\(^{14}\) Chapter I, Article 2, point 8, p.26  
\(^{15}\) Chapter X, Article 2, p.57
The Regulation should limit the scope of IMPs to treatments that are truly investigational and exclude therapies and references which are being used in studies for their licensed purpose or are standard treatments.

**Safety reporting**
The Regulation has consolidated several aspects of safety reporting legislation and contains provisions to support electronic submissions. Annex III of the Regulation contains information on reporting of Serious Adverse Events (SAE) by the Sponsor.\(^{16}\) Much of the legislation on safety reporting had been replicated from existing CT3 guidance.

**Annual Reporting by the Sponsor to the Agency**
The Regulation states that annual reports must be produced for trials for non-authorised products and products that are used outside the terms of their licence.\(^{17}\) The inclusion of products used outside of their licence raises certain issues for reporting safety, which mainly concern the fact that marketing authorisations are rarely kept up-to-date with standard practice:

- Standard practice often includes comparator products that are used outside the terms of their marketing authorisation.
- Many multi-drug regimens that have been established as the standard treatment for a particular indication include at least one drug that is not licensed for that indication.
- A trial may only involve drugs that are broadly used within the terms of their licence (i.e. licensed for a particular type of cancer and used for another type of cancer).
- Drugs may be used either precisely or broadly within the terms of the licence, but are used in a new combination.

Clarification on how the new Regulation will apply to these circumstances is required.

**Annual Reporting by the Sponsor to the Marketing Authorisation Holder**
Under the Regulation, sponsors must inform marketing authorisation holders of all serious adverse reactions (SARs) related to a product that is used within the terms of its licence.\(^ {18}\) Often, such products are sourced from trial sites’ own stock, therefore, multiple brands can be administered to patients within a trial. In addition, the brand name or manufacturer is not always made available to a sponsor. It will be very difficult for sponsors to comply with this clause in this situation.

In addition, the clause does not specifically reference investigational medicinal products, therefore further clarity is needed to establish whether this requirement will also apply to auxiliary medicinal products.

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\(^{16}\) Annex III, p.79

\(^{17}\) Chapter VII, Article 39 (p.50)

\(^{18}\) Chapter VII, Article 41 (p.51)
Other reporting obligations relevant subject safety
Sponsors are required to report ‘unexpected events which affect the benefit-risk balance of the clinical trial, but are not suspected unexpected serious adverse reactions’. It is unclear as to what these events would be if they are not SUSARs. In addition, non-serious unexpected adverse reactions would fall into this category.

The Reporting of Serious Adverse Events After Trial Closure
The annex of the Regulation states that serious adverse events must be reported by investigators to sponsors after the end of the trial. Currently, investigators are only required to submit unexpected serious adverse reactions. Extending reporting to all serious events has the potential to place a huge administrative burden on investigators and sponsors and it is unclear as to what the purpose of this requirement is. It will not enhance patient safety.

Reference Safety Information
The Regulation states that the Reference Safety Information is contained in the Summary of Product Characteristics or Investigator Brochure (as is currently stated in CT-3). Sponsors can currently apply for authorisation for part, or all, of the RSI to be contained in trial protocols. This is essential for established multi-drug regimens or multi-modal treatments (for example drugs plus radiotherapy) where the list of undesirable effects in the SPC is not in line with experience of treatments obtained from routine clinical practice. It is essential that this provision will continue, as restricting RSI to that contained in SPCs will result in the unnecessary over-reporting of SUSARs.

Recommendations
3. **Elements of the safety reporting system should be clarified and reconsidered in order to streamline reporting to benefit both patients and trialists**
   - The requirements for annual reporting by the sponsor to the Marketing Authorisation holder should be removed.
   - Reporting serious events after trial closure should be clarified, as it has the potential to cause significant administrative burdens.
   - Sponsors should be able to include Reference Safety Information in the protocol that is not part of the Summary of Product Characteristics.

Substantial modifications (previously substantial amendments)

Submitting substantial modifications
The guidance on what qualifies as a substantial modification provides less clarification than that of a substantial amendment in the previous Directive and guidance. The lack of a definition of what constitutes a non-substantial amendment is a concern as it does not give an indication of when a change needs to be submitted to the portal.

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19 Chapter VIII Article 50 (p.53)
20 Annex III, article 4, p.79
21 Annex III, article 11, p.80
We believe that the Regulation possibly reduces the responsibility of a sponsor to assess whether a modification to a trial should be considered substantial.\textsuperscript{22} Due to unclear definitions and processes, sponsors may feel that they would need to submit all changes to the trial protocol to be assessed by the regulator whether it is considered substantial or not. This would create significant amounts of extra work for Member States, sponsors and trialists and would cause delays and additional bureaucracy. We believe that the definition of a substantial modification is intended to be more limited under the Regulation, which is welcomed, but the definition itself and the decision and assessment process under the proposed legislation are now unclear and potentially problematic.

Further issues arise from the short timelines for response if additional information is requested from the sponsor. The current Regulation states that requests for information must be met within six days, this could represent a challenge for academic trials units’ resources.

\textbf{Presumed approval}

Throughout the document, there has been a change in emphasis to assuming that an amendment or initial approval would be granted when a Member State does not respond within stated timelines.\textsuperscript{23} However, we would prefer to have confirmation that they can proceed and we are unsure how significantly presumed approval would affect the running of clinical trials.

\textbf{Recommendations}

4. \textit{We would like further revision to ensure more emphasis is placed on the sponsor to decide whether to report substantial modifications.}

- More core guidance is needed to clarify the definitions around substantial modifications. There should be a clear definition of what constitutes a substantial modification and what does not.
- The process should be made clear on what happens if a sponsor fails to submit a modification which is later deemed substantial by regulators.

\textbf{Co-sponsorship}

It is a positive step that co-sponsorship has been formally recognised and legislated for at the EU level.\textsuperscript{24} Cancer Research UK welcomes this development and believes it will support academic trials across Europe. Co-sponsorship currently takes place in the UK and other European countries; it allows allocation of the sponsors’ responsibilities between two or more institutions (co-sponsors) or joint responsibility shared by institutions. Sharing responsibility allows institutions and organisations which are not capable of taking on the full liability of sponsoring a trial to participate and share responsibility with other organisations. As Cancer Research UK has stated previously, for this approach to be truly effective it needs to be recognised across Member States.

\textsuperscript{22} Chapter III, Article 18 (p.38)
\textsuperscript{23} Chapter III, Article 19 (p.39)
\textsuperscript{24} Chapter XI (p.59)
Recommendation

5. Co-sponsorship should be enshrined as it is set out in the Regulation.

Related legislation and guidance documentation

Existing guidance documentation
It appears that the Regulation replaces existing detailed guidance documentation on the conduct of clinical trials such as CT1 and CT3, and the EU GCP Directive (2005/28/EC). We would welcome clarity from the Commission on whether this is the case.

Declaration of Helsinki
The explanatory memorandum preceding the Regulation refers specifically to the 2008 version of the Declaration of Helsinki.\textsuperscript{25} The use of this version of the statement may be problematic due to the requirement listed in Article 35 of the Declaration which requires patients to ‘be assured of access to the best proven intervention arising from the study’.\textsuperscript{26} If mandated, this may cause significant problems for running clinical trials.

Paediatric trials
We need to understand if this Regulation is going to supersede existing guidance relating to paediatric trials and what possible relationship they could have. The issues highlighted in this document are confounded by the fact that most paediatric treatments, especially in Cancer, are not used within their licensed indications. There are also substantive differences in standard treatment/clinical practice across the Member States.

We are also concerned about point h in Article 31 which states that a paediatric trial must have some direct benefit for the group of patients involved.\textsuperscript{27} This is a concern as diagnostic trials or similar studies do not immediately confer a benefit on the participants but will help to build knowledge to support care in the future.

Recommendation

6. We would welcome further clarity on how the Regulation relates to existing pieces of clinical trials legislation.

National indemnification scheme
This scheme adds a requirement for Member States to create national indemnification schemes for compensation coverage, which it is hoped will provide a more affordable way for sites running studies to gain indemnification.\textsuperscript{28} This could particularly help with the set up of trials in Member States, where previously indemnity was provided by individual institutions. Cancer Research UK believes that patients involved in trials will be covered by the NHS indemnification scheme in the

\textsuperscript{25} Introduction point 63 (p.24)  
\textsuperscript{26} WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects, article 35  
\textsuperscript{27} Chapter V, Article 31, 1h (p.47)  
\textsuperscript{28} Chapter XII, Article 73 (p.60)
UK, but clarification is required. The proposed scheme appears to relate to negligence; there needs to be clarity on the provision of 'no fault' or non-negligent harm compensation to subjects. This regulation does not appear to take away from the requirement of the sponsor to indemnify the study which can also be prohibitive in high risk groups of patients (e.g. some paediatric studies and obstetric studies). There are also operational issues of how a Member State could afford and maintain such a scheme.

Recommendations

7. **Further detail on the scope and flexibility of the national indemnity scheme need to be outlined.**
Annex I: Key calls from Cancer Research UK’s previous report: Supporting research, protecting patients: Cancer Research UK’s recommendations to reform the Clinical Trials Directive

The key calls for Cancer Research UK in the 2012 report Supporting Research, Protecting Patients calling for the revision of the Clinical Trials Directive were:

- Retain the function of national competent authorities in regulating single country trials with multinational trials having the option to participate in a Co-ordinated Assessment Procedure (CAP).
- The definition of an Investigational Medicinal Product should be limited to include only therapies which are genuinely investigational and novel.
- The Directive should allow for a risk-based approach to the assessment of clinical trials, ideally with the onus on the sponsor to justify the assessment.
- Substantial amendments should be limited to changes that affect patient safety or the scientific outcome of a trial, as opposed to reporting purely administrative amendments.
- The safety reporting system should be overhauled so that SUSARs are reported in a manner which directly contributes to patient safety.
- Multiple organisations should be allowed to sponsor clinical trials in order for risk and responsibility to be shared and facilitate further collaborative working.

We would be happy to provide any further information or an expert to discuss these issues further, as required. Please contact Daniel Bridge on daniel.bridge@cancer.org.uk or telephone 0203 469 8153.