

Cancer Research UK submission to the European Commission Concept Paper on revision of the 'Clinical Trials Directive' 2001/20/EC

May 2011

Summary

Cancer Research UK welcomes the opportunity to respond to this consultation.

We welcomed the aims of the Clinical Trials Directive when it was introduced, but feel these aims have not been realised. As we have outlined in previous submissions to the Commission, it is essential that the European Commission, together with the National Competent Authorities, develop a harmonised and proportionate regulatory framework for clinical trials.

Key Recommendations

- **Adopting a proportionate approach:** Revision of Directive should address the lack of proportionality across all aspects of clinical trial regulation – including clinical trial assessment, authorisation and monitoring. We would welcome the introduction of a proportionate approach to the assessment and regulatory requirements of clinical trials, ideally with the onus on the Sponsor to justify the assessment. This should take into account a number of factors including the extent of prior knowledge and experience with the Investigational Medicinal Product (IMP) and the patient population involved. There has not yet been a proposal laid out as to how to achieve this, therefore making commenting on other proposed revisions to the Directive challenging.
- **Streamlined authorisation and assessment of clinical trials:** We are broadly supportive of the approach outlined in the recent concept paper from the Commission on having a single 'EU portal' for submitting documentation for multi-national trials. It could reduce the administrative burden of multiple submissions at the time of initial application as well as amendment and clinical study reporting. However, we would like to see a full impact assessment to be reassured that this proposal would not lead to increased cost or approval times. We are supportive of the principle behind the proposal for a 'coordinated assessment procedure' (CAP) that would allow all Member States to input into application assessments but would have a lead 'Reporting Member State'. However, until there is more detail as to how this would operate in practice, it is difficult to be strongly supportive of the proposal.
- **Scope and definitions:** It is essential that the scope of the Directive is applied in the same way across Member States. The lack of clarity of the definitions included in the Directive contributes to its inconsistent implementation across Member States. Where the regulatory requirements are unclear there is evidence that those undertaking trials go above and beyond the requirements to ensure that they are compliant. The definitions that determine the scope of the Directive should be revised to ensure that studies are treated consistently across Member States.

- **Simplified approval and monitoring requirements:** The Directive sets out specific requirements for safety reporting for UK trials including reporting all suspected unexpected serious adverse reactions (SUSARs) to the National Competent Authority (the MHRA¹ in the UK), the main research ethics committee and the national competent authorities of any other Member State where the trial is being conducted. Sponsors are also required to submit an annual safety report to both the National Competent Authority and relevant ethics committee. These arrangements lead to unnecessary duplication, without enhancing patient safety. The Commission's concept paper has not identified how these requirements could be revised and we would like greater clarity on how these arrangements could be simplified.
- **Co-sponsorship:** Through the experience of our non-commercial clinical trials units we have found benefit from the current UK regulatory approach that allows allocation of the sponsors responsibilities between two or more institutions (co-sponsors) or joint responsibility shared by institutions. We support this approach and would value recognition of these models throughout the EU.

Acknowledgements

Our response has been collated following internal staff discussion and with contributions from the following additional groups/individuals:

- Cancer Research UK and UCL Cancer Trials Centre (CTC)
- Cancer Research UK Liverpool Clinical Trials Unit (LCTU)
- Cancer Research UK Clinical Trials Unit Glasgow
- Cancer Research UK and University of Southampton Clinical Trials Unit
- Cancer Research UK Clinical Trials and Statistics Unit (ICR- CTSU)
- Cancer Research UK Wales Clinical Trials Unit (WCTU)
- Cancer Research UK Clinical Trials Unit Birmingham (CRCTU) including the Children Cancer Trials Team (CCTT)
- Peter Johnson, Chief Clinician, Cancer Research UK

This response does not represent the views of any one individual or organisation listed above, but is the product of a collaboration between all listed parties.

Response to consultation questions

Consultation Question 1:

We are broadly supportive of this approach to deliver a mechanism that would enable the application for a multinational clinical trial to be submitted jointly to all Member States concerned. If appropriately resourced and supported this could reduce the administrative burden of multiple submissions at the time of initial application for clinical trials authorisation, but also when submitting protocol amendments and Clinical Study Reports. We would like to reiterate the importance of maintaining submission to the relevant National Competent Authority for single country trials, and would not endorse a move to a centralised European process for single country trials.

We feel that there has not been a sufficient evaluation of the impact that this process would have on timescales for application, and we would not want to see any increase in the time taken to apply for authorisation. In order for a centralised submission to be effective there is

¹ Medicines and Healthcare products Regulatory Authority (MHRA)

a need for a harmonisation of the CTA documentation package, in order to eliminate the drain on resources currently experienced due to the differences in documentation required by the differing member states. We would not wish to see the documentation requirements increased as a result just to ensure current requirements of all Member States are covered irrespective of the country in which the CTA is submitted. We would want to see the harmonised package to be limited to essential documentation to support the CTA application.

The resource and infrastructure implications of implementing and running this type of centralised application system for multinational trials need to be carefully considered. We would be concerned about any costs a non-commercial trials unit may incur as a result of the implementation of this system e.g. if formal training were to be required prior to being able to access the system.

We would also like to see an assessment of how this single 'EU portal' would then align with application systems in Member States that are used for other aspects of clinical trial approvals. For example, in the UK the Integrated Research Application System (IRAS) currently is the central portal for submission of all regulatory aspects of research applications, including applications to the UK National Competent Authority, the Medicines and Healthcare Regulatory Agency (MHRA). We would be concerned if there was not alignment of these two systems, as it could potentially increase the administrative requirements associated with submitting studies for authorisation.

Based on all of our above comments we would like to see a clear proposal from the Commission as to how a single portal submission for multinational trials would work in practice.

Consultation Question 2:

We agree with the Commission's appraisal that the assessment of the information submitted through the 'EU portal' should not then be done independently by each Member State involved. An approach which still allowed for independent assessment of multinational studies would not prevent divergent approaches to authorisation, and the resultant cost and administrative burden on sponsors would be excessive.

Consultation Question 3:

We agree with the Commission's appraisal that assessment for multinational trials via a central scientific committee would not be appropriate, as we anticipate that this would lead to delays in obtaining approvals due to the nature of committees only being able to meet at fixed times. The costs to facilitate such a committee, which would no doubt be fed back to the applicants, would also make this an unworkable solution.

Consultation Question 4:

We are supportive of the principle behind the proposal for a 'coordinated assessment procedure' (CAP) that would allow all Member States to input into application assessments but would have a lead 'Reporting Member State'. However, until there is more detail as to how this would operate in practice it is difficult to comment on whether this would lead to a reduction in times and costs in order to administrate this approach.

We have concerns as to the level of input that Member States participating in a trial would still request to have in relation to assessment decisions, as if there is not sufficient harmonisation across all aspects of the Directive then there could remain significant divergence of opinions. We would favour the 'Reporting Member State' to take a very strong lead as the main assessor of applications.

Elements of the catalogue appear incomplete, and in parts contradictory. For example, reference is made to: 'under the CAP, it would be up to each MS to divide the tasks between CNA and EC'. However, the remit of ECs are well established, and by introducing potential for Member States to interpret the division of tasks between ECs and CNAs it is difficult to see how this could lead to a more harmonised approach. We would suggest that the proposed split in responsibilities between the CAP and ethics should be similar to that already established in the UK. In the UK the role of the competent authority is to protect public health by ensuring that CTIMPs meet the required regulatory standards with respect to quality and safety and to review CTA applications to ensure that sufficient, appropriate data are available to support the proposed clinical trial and that planned safety monitoring and reporting procedures are adequate.

We would like to see the following questions addressed in a more detailed proposal on CAP from the Commission:

- How would the 'Reporting Member State' for a submission be chosen – would it be the country of the trial sponsor or would EMA choose?
- What would be the impact on fees – currently there are not standardised fees across MS. Would additional fees be payable to support the administrative involvement of the EMA to support the CAP system?
- As proposed the timelines for CAP approval allow up to 60 days for a CAP decision and then this would feed into a single decision from the MS on the trial. Currently under UK legislation an initial response (potentially an approval or request for more information) is received from MHRA within 30 days. Would the timelines for trials conducted in the UK therefore increase if they were multinational and ran through CAP?
- How would scientific advice from one MS be viewed if the 'Reporting Member State' on the final application was from a different MS?
- What will be the process to allow additional MSs to be added after CTA approval?
- How would CAP work in relation to amendments?

Consultation Question 5:

Please see our response to consultation question 4.

In addition we would like to add that knowledge of product and normal clinical practice (listed under a) will vary between MS and therefore discussion of these in centralised forum would be beneficial as it will increase generalised understanding of products and care.

Consultation Question 6:

We favour the option to opt-out, with the following caveats. If an individual country has concerns about a trial which precludes them participating, they must be able to opt out and the sponsor kept informed of reasons. The sponsor must be allowed opportunity to address concerns of a MS, particularly for example where the MS 'opting out' would have been essential to the conduct of the trial. A decision to opt out (and the concerns raised) should be passed on to the Commission or EMA. Unresolved issues should then be referred to EU level decision and heard by an independent body – which would also be responsible for part of the monitoring and oversight of the conduct of CAP.

Consultation Question 7:

It is difficult to respond to this question given the number of outstanding questions relating to the CAP procedure outlined in our response to the previous questions.

On the one hand, if CAP is optional for all trials then this could lead to confusion as applicants will choose different approval routes based on perceived speed of obtaining

approval, and there is less scope for harmonisation (CAP is a delivery mechanism for harmonisation). However, without a more detailed proposal and initial impact assessment of CAP, it would be difficult to support a model where CAP becomes mandatory for all clinical trials, including single country. At this stage we also feel that there are too many unknowns to support mandatory use of CAP for all multinational trials, although if proven to be a successful system this is the direction we would like to see CAP moving in. Therefore, at this stage in the process we are supportive of CAP being optional to all trials, and in the first few years would support CAP only being a process for multinational trials to ensure that the mechanisms for this were fully developed before an option to submit for single country trials became available.

Consultation Question 8:

The appraisal that the Commission has outlined here only looks at one element of risk-classification of trials (type A), and only looks at how a proportionate approach could be applied to the initial assessment of these trials. A bigger issue for Cancer Research UK is the resource requirements pre-application and during the trial (data collection and monitoring) which this partial proposal for a proportionate approach does not address.

We welcome the concept of 'type A' trials being identified at pre-assessment and resulting in reduced timelines. However, there is a need for clarity as to where the responsibility for determining whether a trial is class A lies – would it be with the sponsor or as part of the CAP procedure?

Consultation Question 9:

We agree that the preferred approach would be to have a more proportionate approach to the application of all elements of the requirements set out in the Clinical Trials Directive (and therefore inspection). This proportionate approach should take into account the risk of the trial to the patient, including the information already known about the trial treatment and the research questions being addressed, and allow implementation of procedures (e.g. TMF content, IMP labelling and accountability, monitoring etc) that are commensurate to this.

A certain number of risk levels for trials should be defined by the Commission with associated proportionate requirements for CTA application, and then during a trial this risk can be further defined. Under this model, as part of the initial application a Sponsor could propose the level of risk for a specific trial (based on the Commissions guidelines) with associated justification etc. If accepted by the authorisation decision-maker then the acceptable level of monitoring etc during the trial would then be defined. The competent authority would also have the option to disagree with the risk rating during CTA review and include a revised rating in the final approval/assessment. This could potentially harmonise the approach across Europe but provide a mechanism to consider trials in a proportionate manner.

We feel that a sufficient proposal for a proportionate approach and a mechanism for harmonising this across MSs has not been sufficiently laid out by the Commission. As such we do not think the option to consider limiting the scope of the Directive thereby excluding more studies should be completely dismissed, and that further assessment of this option should be undertaken.

Consultation Question 10:

We agree with the Commissions appraisal that the scope of the Directive should not be limited to commercial sponsors. The application of the Directive should vary according to trial risk, not who the sponsor of the trial is, therefore emphasising the importance of developing a detailed proposal for a proportionate approach. However, there should be some recognition that not all sponsors are licence holders or involved in the manufacturing or

marketing of IMPs – which is relevant when looking at requirements to maintain the IB and SmPC.

Consultation Question 11:

We agree with the concept laid out by the Commission, but would like to see a more detailed proposal. We feel that there is a risk that detailed provisions could add to the bureaucratic burden and cost of trial conduct if an appropriate proportionate approach is not developed alongside this. The research community should be given the opportunity to comment on how the level of risk is categorised and how approaches to trial conduct could be adapted to be commensurate to risk.

Consultation Question 12:

The Directive sets out specific requirements for safety reporting which currently lead to duplication between EU Member States as well as between National Competent Authorities and ethics committee(s) within a single Member State. The lack of clarity in the definition of Suspected Unexpected Serious Adverse Reactions (SUSARs), and inconsistencies in reporting requirements across Member States, may lead to both over-reporting and under-reporting. We would therefore like to see the definition and requirements for SUSAR reporting evaluated, and clarified.

Consultation Question 13:

We agree that there has been sufficient evidence provided to both the Commission, and also the recent Academy of Medical Sciences review of regulation and governance of health research, to warrant a clarification of the definition of an Investigational Medicinal Product. In addition to the change of definition there is also a need for clearer guidance on what constitutes an IMP. One route for achieving this is through updating the guidance on NIMPs, in particular to ensure any requirements for accountability are commensurate with nature and status of the product, and in particular where licensed product in routine use that standard hospital practise may apply.

We are concerned that the suggested wording for changing the definition could actually further broaden the spectrum as to what is considered an IMP under the Directive. The definition needs to clarify that drugs used as reference in a clinical trial, should not be classed as an IMP because they will follow the current standard of care, and therefore, should be classed as an ‘auxiliary medicinal product’. In addition, we would like clarification that drugs which are already licensed and routinely used for both licensed and unlicensed indications (at doses/schedules close to their licensed indication), do not qualify as an IMP.

We support the notion that there should be alternative procedures (IMP management and safety reporting) for drugs that may not be licensed for use in a particular setting but that have been used as standard care for many years. We would suggest that drugs that do not require particular manufacture or packaging (i.e. are supplied directly from hospital stock) should not require detailed accountability records or even destruction logs.

The appraisal refers to dossier requirements and labelling for ‘auxiliary medicinal products’, which acts as a further clarification to what is classed as an IMP or NIMP. There are currently no labelling requirements for NIMPs, and it will be important that this is also the case for ‘auxiliary medicinal products’.

Consultation Question 14:

When the CTD came in and was implemented across the Member States there was a big disparity in relation to insurance. Many of the Member States have already made it compulsory for the sponsor to have insurance for the clinical trials. The UK is one of the few countries where insurance is currently not compulsory for trials, although it is a requirement

of Ethics Committees to ensure that there is adequate insurance/indemnification for trial subjects.

The current insurance and indemnity position in the UK is challenging for NHS organisations as they are only entitled to self fund a clinical negligence scheme. They cannot currently take out insurance for the rest of the trial responsibilities and hence they have to enter into a co-sponsorship arrangement, often with universities, so that they can buy the extended insurance (please see response to Consultation Question 15).

We support the route of optional indemnisation by Member State placing Member States under obligation to provide for an indemnisation for damages incurred during clinical trials performed in their territory taking account the national legal system for liability. It will be essential for the Commission to provide clarification on the required terms of clinical trials insurance policy. In addition to this approach we also support the principle of further stratifying insurance/indemnity requirements based on a proportionate approach (i.e. we do not see these options as mutually exclusive), however we have not yet seen a detailed proposal for such an approach.

Consultation Question 15:

Our experience as a sponsor of smaller early phase trials has been that it has not been difficult to have a single Sponsor for UK-only trials. We feel that this has given clarity and accountability to a named organisation for patient safety. As a non-commercial organisation it was felt that a single Sponsor should be no more difficult for us than anyone else. Single Sponsor concept supports the oversight of a safety in multiple sites.

However, through the experience of our non-commercial clinical trials units we have found benefit from the current UK regulatory approach that allows allocation of the sponsors responsibilities between two or more institutions (co-sponsors) or joint responsibility shared by institutions. We support this approach and would value recognition of these models throughout the EU. We have found this approach to be essential across many of our academic trials units, examples highlighted to us include when seeking international collaboration, multi-national paediatric trials and early phase drug trials. For some of our trials units the co-sponsorship model represents a significant number of trials that are run – the Institute of Cancer Research clinical trials unit is currently running 11 co-sponsored trials, 1 of which will run internationally. This represents over 7250 patients recruited onto these trials from over 500 participating sites.

We have outlined one specific example of the value of the co-sponsorship model in the box below.

Case Study: Cancer Research UK Clinical Trials Unit Glasgow

The majority of trials coordinated by the Cancer Research UK Clinical Trials Unit in Glasgow are co-sponsored by NHS Greater Glasgow & Clyde (NHSGG&C) and the University of Glasgow (GU), two organisations which are closely aligned.

For each clinical trial co-sponsored by the NHSGG&C and GU, prior to study initiation, a non-commercial funded clinical trial agreement is put in place between them. The roles and liabilities each organisation will take under the Medicines for Human Use (Clinical Trial) Regulations 2004 are laid out in this agreement, which is signed by both organisations.

In summary, in this agreement the GU is responsible for carrying out the obligations,

responsibilities and is deemed the “sponsor” for the purposes of Part 3 of the regulations, and NHSGG&C is responsible for carrying out the obligations and responsibilities and is deemed the “sponsor” for the purposes of Parts 4, 5, 6 and 7 of the regulations. Effectively, therefore, the two organisations share the role of sponsor.

This arrangement is only required either when the investigator is external to Glasgow or is an employee of GU; otherwise NHSGG&C can act as a single sponsor. Currently half of the trials run through the Cancer Research UK Clinical Trials Unit in Glasgow have external Chief Investigators or are Chief Investigators employed by GU.

For trials that involve international collaboration the co-sponsors/sponsor are not in a position to take on role of sponsor outside the UK (either in EU or non EU countries) as they cannot provide effective sponsor’s oversight. In this instance a local sponsor in the country is appointed to ensure local regulations are met and to have oversight of the local trials organisation who are coordinating the trial. Agreements are put in place between the co-sponsors and the local sponsor in each participating country that clearly documents the roles and responsibilities of each party. If the concept of sharing sponsor responsibilities with a local sponsor in each participating country was not allowed it would make it impossible for us to run international trials.

We agree that there needs to be greater clarity of the role of the EU legal representative to facilitate multi-national conduct where the sponsor is a third country entity. The UK CA clarifies that the EU legal representative should be willing to act as the agent of the sponsor in the event of any legal proceedings instituted in the EU but does not assume any of the legal liabilities for the trial and does not therefore require insurance or indemnity to meet such liabilities. We support a wider acceptance of this approach.

Consultation Question 16:

Cancer Research UK does not have any evidence relating to this.

Consultation Question 17:

Cancer Research UK does not have any evidence relating to this. We do not have specific experience of this, but strongly support the EU commitment to support fundamental human rights for all trial participants.

Consultation Question 18:

For more data, analysis and case studies please refer to Chapter 5 of the Academy of Medical Sciences report, ‘A new pathway for the regulation and governance of health research’.²

About Cancer Research UK

Cancer Research UK³ is leading the world in finding new ways to prevent, diagnose and treat cancer. We are the largest independent funder of cancer research in Europe. Over half of all cancer research in the UK is carried out by our doctors and scientists. CR-UK’s work is entirely funded by the public and in 2009/10, we spent £334 million (€400 million) on research, supporting the work of more than 4,000 scientists, doctors and nurses.

² Academy of Medical Sciences (2011). *A new pathway for the regulation and governance of medical research*.

³ Registered charity no. 1089464

Cancer Research UK funds research into all aspects of cancer from exploratory biology to clinical trials of novel and existing drugs as well as population-based studies and prevention research. We are involved with all stages of clinical trials, and we have a perspective both as a funder of academics conducting trials and as a Sponsor of early phase trials. While we are a mainly UK organisation, our world-class scientists, doctors and nurses collaborate with cancer experts in over 50 countries, working together to fight cancer, and have contributed to most of the world's top cancer drugs, including tamoxifen, herceptin and temozolomide.

Cancer Research UK has increasingly become involved in international research collaborations, some driven by Cancer Research UK scientists (e.g. genome-wide association studies and epidemiology studies) and others where we engage as international partners (e.g. International Cancer Genome Consortium (ICGC), EU initiatives). Clinical trials are very often international and are likely to become increasingly so as we identify smaller patient subsets of different cancer types. However, Cancer Research UK usually only funds the UK component of an international clinical trial.

Currently, CR-UK's clinical trials team manages the budget and administration of 8 Clinical Trials Units across the UK and provides funding for Senior Research Nurses. The team also provides secretariat support for our Clinical Trials Awards and Advisory Committee (CTAAC), which currently funds more than 250 studies. These range from large scale phase III clinical trials, to support for feasibility and/or pilot studies, as well as some phase II studies. In addition, the clinical trials team contributes to strategic oversight support for late phase trial activities in the UK. Although we solely fund activities in the UK, many of our trials are international and the Clinical Trials Units that we support have experience running international studies, for which the host institutions act as Sponsor.

Our Drug Development Office (DDO) seeks to develop new treatments for cancer patients. The Office manages and executes drug development programmes from exploratory and preclinical development through to designing, conducting and monitoring high quality, ethical, early phase clinical trials. By working closely with leading UK scientists and clinicians, the DDO offers both academia and industry a mechanism for developing novel anti-cancer agents through their managements of Phase I and Phase II clinical studies. The clinical studies are carried out within the UK only, within a network of specialist cancer centres. All trials undertaken by the DDO are sponsored by CR-UK.

CR-UK began funding trials in 1988, and since 1995 this has been through 'response mode' funding whereby any UK academic can apply for support from the Charity. Since 1988 we have funded almost 300 therapeutic trials and more than 100,000 patients have taken part in these trials. In the same time period the DDO has sponsored and conducted over 100 early phase exploratory studies, with more than 2,000 patients entered on these trials. These exploratory studies were on new clinical agents, of which five have been taken to market by subsequent business partners.

Data sourced from the UK Clinical Research Network (UKCRN) demonstrates that year on year, since 2005, the number of patients on CR-UK supported trials has continued to increase and now stands at over 28,000. Throughout this same period, CR-UK trials accounted for nearly 70% of all recruitment to academic cancer trials in the UK, whilst the charity's contribution to randomised controlled trials exceeded 80%. In total 34,000 cancer patients and other participants entered a trial funded or endorsed by CR-UK last year.

We often work in partnership on our clinical trials portfolio, including with the Department of Health (DH) (primarily through the provision of NHS Service Support and Treatment costs), the National Cancer Research Network (NCRN) infrastructure and increasingly the

Experimental Cancer Medicine Centres (co-funded by DH and CR-UK), the Medical Research Council, the European Organisation for Research and Treatment of Cancer (EORTC), the Leukaemia Research Fund, and the pharmaceutical industry.

We hope you find our comments useful. We would be happy to provide any further information or a representative to discuss the response further, as required. Please contact Emma Greenwood, Policy Researcher at Emma.Greenwood@cancer.org.uk or on 0044 (0)20 3469 8358; or Layla Theiner, Public Affairs Manager (EU) at Layla.Theiner@cancer.org.uk or on 0044 (0)20 3469 8127.