Cancer Research UK submission to the European Commission assessment of the functioning of the "Clinical Trials Directive" 2001/20/EC

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About Cancer Research UK

Cancer Research UK (CR-UK)[1] is leading the world in finding new ways to prevent, diagnose and treat cancer. We are the world's leading charity dedicated to cancer research and 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. Cancer Research UK's work is entirely funded by the public and in 2008/09 we spent £355 million on research, supporting the work of more than 4,500 scientists, doctors and nurses.

CR-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. Our scientists, doctors and nurses have contributed to the development of 19 of the top 20 drugs used to treat cancer patients worldwide today.

At CR-UK 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.

For further information about our involvement in clinical trials, please see appendix 1. For further information about the implementation of the Clinical Trials Directive (CTD) in the UK, please see appendix 2. For a glossary of terms used throughout this response, please see appendix 3.

Acknowledgements

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

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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.

[1] Registered charity no. 1089464

Summary

We welcome the opportunity to respond to this consultation, and will be submitting a copy of our response to the MHRA.

Overall, we struggled with the style of the consultation document, receiving feedback from several contributors that it was overly complicated and not clearly aligned to the content of the CTD. We would therefore recommend that further consultations relating to the potential revision of the CTD clearly relate each question to specific articles within the Directive, or accompanying guidelines/national legislation.

We welcomed the aims of the CTD when it was introduced, but feel that largely these aims have not been realised. One advance that the CTD has achieved is an improvement in the quality of data resulting from all trials conducted, and this is something that we would not want to lose through any changes to the Directive. However, the CTD has negatively impacted on large academic trials run by Clinical Trials Units (CTUs), evidenced in our response.

We have no evidence that patient safety has increased since the introduction of the CTD; we believe that the level of patient safety was already high. Our key recommendations are therefore focused on the need to improve the conduct of non-commercial trials without having a detrimental impact on the progress we have made in the UK in other areas of trial facilitation.

Key Recommendations

1. The implementation of the CTD has led to increased bureaucracy, cost and time in the setting up of trials, both for single country trials and trials that are run across a number of countries. In part, this is because different Member States (MS) interpret and implement the Directive differently. We would welcome more detailed guidance in a number of areas to improve comprehension of the Directive and with the aim of streamlining the authorisation processes where possible. We would prefer additional guidance to help interpret the CTD, as opposed to regulation.

2. For single country trials, we would support the system where an application can be made with the National Competent Authority (NCA), e.g. the MHRA in the UK.

3. For multi-national trials, we support a system whereby the Sponsor makes the decision about whether to submit an application via a centralised procedure or nationally via a standardised process. In this scenario, we would support the Sponsor country Clinical Trial Authorisation (CTA) decision becoming binding in other MS sites.

4. We would welcome a risk-based approach to assessment of clinical trials, ideally with the onus on the Sponsor to justify the assessment. This should take into account the extent of prior knowledge and experience with the Investigational Medicinal Product (IMP), the patient population involved, whether or not the IMP already holds a marketing authorisation and whether the clinical trial is performed with an authorised medicine in approved indications or for other therapeutic uses. It is vital that the opinions of different patient groups are heard in this process, e.g. those patients at the end of life may have no other mechanism to access certain drugs other than via a clinical trial. This approach would allow for different standards to apply for trials deemed to be lower risk.

5. We do not support a two-standard approach for commercial vs. non-commercial/academic Sponsors. Many academics have indicated that the Doctors and Dentists Exemption (DDX) system was less costly and bureaucratic, and that many large academic trials were conducted under this system that led to standards of care that define our treatment of

cancer. However, given the current environment for clinical trials in the UK, what is needed now is clearer guidance and more efficient implementation of the existing directive via a risk-based approach.

6. We would welcome further guidance on the requirements for substantial amendments and on what constitutes a substantial amendment. The current guidance is unclear and has led to a stop/start approach to conducting trials. Very large numbers of SUSAR reports are sent to all investigators in large trials for little purpose: their sheer volume makes it impossible to do anything other than scan and file them, and the chance of significant patterns being detected is not increased by simply sending them to every site. What is urgently required is central scrutiny and risk assessment by the Sponsor of the trial, which should be able to determine whether to alert investigators or not.

CR-UK data on the impact of the EU Clinical Trials Directive

In 2006 CR-UK carried out a study into the impact of the CTD on the costs and conduct of non-commercial cancer trials in the UK[i]. Directors and senior staff in 8 CTUs were contacted and invited to participate in the study. The findings from the study indicated that the CTD had resulted in a doubling of the cost of running non-commercial cancer clinical trials in the UK and a delay to the start of trials. The lack of central guidance, lack of clarity regarding the interpretation of the guidance notes, and increase in essential documentation and paperwork were causes of major concern. Further, the CTUs were unable or unwilling to open trials in non-UK centres because of the different interpretation of the CTD by member states. CR-UK would look to repeat this study for further data if it would be of use to the Commission.

In addition, our Drug Development Office (DDO) submitted comparison data between 2003 and 2007 to the Impact on Clinical Research of European Legislation (ICREL) study. They found that the average time between protocol finalisation and inclusion of the first patient on a trial increased by nearly 65% from 2003 to 2007, and that there was a need for a staffing increase of 75% for administration of Clinical Trial Applications (CTAs), trial coordination and monitoring, pharmacovigilance (PV) tasks and quality assurance. These additional costs have meant that less funding has been spent directly on getting more patients into trials as it is has been directed towards staffing increases.

Responses to consultation items

Consultation Item No. 1
In our study from 2006, most units felt that sufficient safeguards were already in place prior to the CTD with Independent Safety, Monitoring and Ethics Committees (IDMC) responsible for monitoring trials on a regular basis, and existing stringent review of Serious Adverse Events (SAE) by the Independent Trial Steering Committees, Trial Management Committees and IDMC. However, it was felt that the increased level of paperwork, perceived bureaucracy, and the potential for the Chief Investigator to be held accountable in law may have had a positive effect by curtailing single investigators working alone without the support of a trials unit.

We are of the opinion that if the EudraVigilance database were properly utilised for signal detection of rare adverse reactions this would indeed lead to improvements in patient safety and we would urge the EU to make appropriate use of this valuable resource.

Key Issue No. 1: Multiple and Divergent Assessments of Clinical Trials
Consultation Item No. 2

The Institute of Cancer Research (ICR) is one of the world's foremost independent cancer research organisations. Cancer Research UK provides infrastructure funding for the CTU based there, together with additional funding for trials run from the CTU. Together with colleagues at Imperial College, ICR conducted a number of pan-European trials prior to the introduction of the CTD, and embraced the opportunities international collaboration offered. However, due to the increased complexity, bureaucracy, risk and cost associated with running trials under the CTD, plus the lack of recognition of the co-Sponsorship model (deemed essential by ICR's host institution in order to ameliorate the level of financial risk associated with Sponsorship), no new international collaborations directly involving ICR were developed after May 2004.

When consulting staff at the CTUs we fund, they indicated a noticeable reluctance to start up multi-national trials. The overriding issue is that institutions are struggling to act as Sponsor due to the inconsistent interpretation of the term Sponsor in different EU member states. Our CTU in Birmingham has until quite recently only been involved in multinational trials taking part in the UK and the Republic of Ireland – as these nations have almost identical regulatory requirements. Their lack of involvement in international research has primarily been due to the difficulty and cost of obtaining indemnity in other Member States but it also reflects problems naming one academic organisation to act as the International Sponsor and the difficulties of arranging contracts applicable to international law (this specific issue lead to a delay of 30 months for one trial opening to recruitment of patients in the Republic of Ireland.) This CTU is only now in the process of taking over responsibility for a number of multinational trials and they have experienced some of the difficulties associated with obtaining authorisation in different Member States.

Another example of differing National Competent Authority (NCA) requirements is highlighted by the paediatric EuroNet-PHL-C1 trial for which the number of Investigational Medicinal Products (IMPs) included on the Clinical Trials Authorisation (CTA) in different Member States varies from as many as 14 to as few as 2. This inconsistency demonstrates a lack of understanding of the definition of an IMP by NCAs and researchers alike.

EORTC has reported that the number of new trials dropped from 38 in 2001, to 19 in 2004, to 7 in 2005; trial costs have increased by 85% and trial initiation was five months slower[ii].

Following the implementation of the CTD at the national level it was widely acknowledged by the CTUs that we supported that there was an increased need for staff to deal with the impact of the changes. An example from one of the CTUs we fund is an increase of essential regulatory staff of 600%[iii] in the period from May 2005 to the present, simply to handle the increased paperwork and expertise required.

Large academic institutions in different countries have a history of collaborating with each other to run multinational trials, especially in rare disease sites and paediatrics, but it is difficult to persuade any one organisation to take legal responsibility for this type of academic endeavour. Consequently, to work around this different countries have taken to running similar related trials each with their own protocol for which a planned meta-analysis of the data is included within the protocol. However, some Member States refuse to approve such activity because of the lack of an International Sponsor. If the requirement for an International Sponsor for this type of activity were to be stringently imposed this could further threaten international collaboration which could have serious ramifications for research in rare disease sites and paediatrics. It also undermines the aim of the Commission's Research Framework Programme, to provide equal access and fair treatment for all interested parties across the European Union.

CR-UK responded to the negative impact of the CTD on the CTUs by providing an additional £750,000 per annum from 1st April 2006 to 6 of our CTUs to support staff posts that dealt with pharmacovigilance, regulatory affairs, IT and contracts. This increase in funding did not correlate with an increase in the number of patients in trials, or increased patient safety.

Consultation Item No. 3
From the study that CR-UK conducted in 2006 we have examples where the comparisons of the overall costs of similar late phase trials run in units before and after the introduction of the Directive were made:

- Example 1: Comparison of two breast cancer trials – overall cost before CTD of £171,713 per annum, overall cost after the CTD of £282,409 per annum.
- Example 2: Comparison of two colorectal cancer trials – overall costs before CTD of £117,458 per annum, overall cost after the CTD of £201,061 per annum.

This demonstrates a doubling of costs which has been independently verified by a non-UK funder of non-commercial clinical trials, EORTC.

In our 2006 study further cost assessments were made of the CTU portfolios before and after the implementation of the Directive. These changes can be quantified both in staff time and indirect costs. For example, during pre-submission of a trial to MHRA, CTU staff reported that it was taking up to 6 months longer for a Trial Co-ordinator to prepare the CTA, Investigator Brochure (IB) and Multi-Centre Research Ethics Committees (MREC) submissions, equivalent to a staff cost of approximately £20,000 per trial. Setting up and logging trial agreements between the Sponsors and all participating centres was a new activity; 4 CTUs had allocated a full time member of staff to work on this issue at a staff cost of up to £30,000 per unit.

The staff and resource costs attributable to starting up and running trials, including visiting all centres and producing a written report, running local launch meetings to ensure that training requirements were met, and conducting monitoring visits, were estimated at being between £60,000 to £100,000 per trial.

The delays to starting a trial as a direct result of the Directive were estimated as between 6 and 12 months.

The DDO at CR-UK submitted a cost analysis to the ICREL report comparing the situation between 2003 and 2007. They found that the average time between protocol finalisation and inclusion of the first patient on a trial increased by nearly 65% from 2003 to 2007, and that there was a need for a staffing increase of 75% for administration of CTA applications, trial coordination and monitoring, PV tasks and quality assurance. However, the DDO is in the position of having a dedicated regulatory resource, and this is not echoed across all academic units we have experience with. It was not felt that this improved patient safety because aspects of patients' safety were already well-addressed through existing structures.

Academic units do not necessarily have the ability to increase capacity to deal with the additional burden of paperwork associated with setting up a trial. For those that have been able to increase capacity it has been at considerable cost, without an associated increase in number of trials set up, or patients recruited. This links into the evidence that DDO submitted to the ICREL study, which demonstrated that costs have increased but there has been no increase in numbers of trials or patients entered into trials. One example demonstrates that pre-CTD several sequential trials were undertaken at a unit, but since the introduction of the CTD their throughput of trials has markedly reduced. This is due to the cost of obtaining MHRA approval dramatically increasing, and increasing monitoring and reporting requirements requiring more staff. One trial at this unit took almost 3 years to be set up.

Consultation Item No. 4

There has already been some attempt at facilitation. However it has as yet not proved to be successful. The Clinical Trials Facilitation Group (CTFG) was established in 2004 by the EU Heads of Medicines Agency (HMA), in order to help co-ordinate the implementation of the EU CTD across member states, particularly for the benefit of multi-national clinical trials. To assist with this, CTFG aims to use various measures including improved data sharing, use of information and communication with stakeholders and other EU working groups. The CTFG launched the Voluntary Harmonisation Procedure (VHP) as a pilot in February 2009, with the aim of facilitating the application process for multi-national clinical trials. Although only some clinical trials qualify at this stage, as of June 2009 only two Sponsors had made use of the VHP.

While we see the benefit of having one streamlined CTA process in Europe, we would support the approach whereby if there is a single country trial, the application can be made with the National Competent Authority (NCA), e.g. the MHRA in the UK. We feel that it would be detrimental for single country trials to have to apply via a centralised mechanism at the European level. However, if a trial was multi-national then we would support a Sponsor decision whether to submit via a centralised procedure or nationally via a standardised process. We support the proposal of the Sponsor country CTA decision becoming binding in other MS sites. There are a couple of practicalities that should be considered when assessing how a centralised approval process for multinational trials would work:

- In academia we do not always know in advance whether a trial will be multi-national. On occasion we may be approached by academics in other member states who are interested in running the trial in their own country once it has opened to recruitment in the UK. We would hope that this type of study could tap into the multinational approval process in some way even though it already has national approval.
- Logistics. We feel that option b would require a centralised electronic application process.
- Cost implications: The resource implications of implementing and running this type of system need to be carefully considered, as we would be concerned about any costs a CTU 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 a new electronic application system.
- We would be concerned if this were to lead to an increase in the approval time frame.

Consultation Item No. 5
We feel that the UK REC system works reasonably well with coordination and timelines, with the exception that the Gene Therapy Advisory Committee partially falls out of this system resulting in additional complications to the process. We already have well established relationships with the MHRA and RECs, and therefore would be cautious of an approach that would damage this existing link.

The option of a 'one-stop shop' for CTA and REC applications is seen as a potentially positive step, as it could reduce some of the timelines associated with the dual process that currently takes place. The UK has already made some progress towards reducing duplication of multiple submissions with the introduction of IRAS. Any new centralised system should therefore take national initiatives such as this into account when developing a new one-stop submission process. It could reduce the administrative burden of multiple submissions at the time of initial application but also with amendments and Clinical Study Reports. However the impact that this would have on timelines is not clear – would it speed the process up or would the review process just default to the longest current review period i.e. ethics? We would therefore recommend that the potential impact of this approach is evaluated, as we are concerned that this might reduce or eliminate the current direct investigator/Sponsor/REC interaction thereby having the opposite effect of increasing bureaucracy and timelines. In addition, we are also concerned about the cost implications of the introduction of a one-stop shop submission process on CTUs.

Key Issue No. 2: Inconsistent Implementation of the CTD
Consultation Item No. 6

We feel that this description is generally accurate. However, would like to make the following observations:

1. With regard to substantial amendments, additions of, or amendments to, a site constitute a substantial amendment but it is not clear from the text whether this type of amendment is included in the figure of 21 000 quoted. In a typical phase III trial it is estimated that for every three amendments to the protocol 27 site amendments will be submitted. This represents a significant administrative burden. We would therefore advocate that notification of this type of amendment be simplified and streamlined if at all possible.
2. With regard to the six-fold increase in SUSAR reporting, although we concur that some of this may be as a result of duplicate reporting we feel that the majority reflects underreporting prior to the implementation of the Clinical Trial Directive. SUSAR reports arising from academic clinical trials are unlikely to have been reported to a NCA prior to May 2004.

With regard to the scope there is still considerable confusion over what constitutes an IMP as illustrated by the EuroNet-PHL-C1 trial. The EU guidance document "Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials" has not resolved this issue.

We agree that there is over-reporting of substantial amendments and suspected unexpected serious adverse reactions (SUSARs). Submitting substantial amendments can have a stop/start effect in an early phase trial, and for large multicentre trials every time a new site joins there is a requirement to complete a substantial amendment process. With up to 200 sites in some of the large trials we fund this is a huge administrative burden, which results in slower patient recruitment rates and increasing trial timelines, with no demonstrable safety benefit. For cancer patients this delay can mean that patients are missing out on potentially life-saving treatments, which are sometimes only available through clinical trials.

In our 2006 study the process for the notification of amendments was viewed as an area of major difficulty. In particular the definition of a 'substantial' amendment had caused concern to most CTUs who had all tried to liaise with MHRA to seek clarity on this issue. Several CTUs mentioned that the change in a Principal Investigator at a participating centre should not be considered as a substantial amendment – this was felt to be time-consuming and to cause unnecessary paperwork and delay.

There needs to be a re-evaluation of what constitutes a substantial amendment and what is simply an administrative change. We would also welcome further guidance and clarity on the requirements for substantial amendments with respect to Chemistry, Manufacturing and Control (CMC) amendments (e.g. shelf-life). The current guidance is unclear and has led to a stop/start approach to conducting early phase trials. We would suggest an approach of "report and go" for certain CMC amendments, with responsibility deferred to the Qualified Person (QP).

Pharmacovigilance (PV) is creating similar blockages in the system. Very large numbers of SUSAR reports are sent to all investigators in large trials for little purpose: their sheer volume makes it impossible to do anything other than scan and file them, and the chance of significant patterns being detected is not increased by simply sending them to every site. What is urgently required is central scrutiny and risk assessment by the Sponsor of the trial, which should be able to determine whether to alert investigators or not. We would also welcome clarity on SUSAR reporting with regards to the following points:

- Where a Sponsor conducts a UK trial on an IMP and a business partner carries out worldwide trials on the same IMP.
- Guidance as to whether UK only trial Sponsors are required to report to Eudravigilance.
- If there is a situation where a business partner in a trial is required to report SUSARs when they are not acting as a Sponsor, but they are leaving that responsibility to trials using the

same drug – who is responsible for the reporting line on SUSARs and how do we avoid duplication?

Another example which may be included is on-site monitoring. As part of the CTA some Member States (e.g. France) have made it a legal requirement to conduct on-site monitoring. In multinational trials, provision has to be made to meet these country specific requirements. However, academic trials are typically funded by a country-specific funding body that may not be willing to pay for these additional costs where these are not considered legally binding in the country in which the funding body reside. Hence additional funding may have to be sought causing delays in the trial opening in some Member States.

Consultation Item No. 7
We do not agree that the current system leads to "insufficient patient protection". From a non-commercial viewpoint we believe the current system has provided clarity by requiring a named overall Sponsor to be responsible for patient safety. The system has tackled issues of conflict of interest and enabled emerging safety issues to be identified and formally communicated to patients earlier. However, we do not have data that demonstrates an overall improved level of patient safety as a result of the CTD.

It is possible that over-reporting of SUSARs could lead to more important events not receiving sufficient attention, which may compromise patient protection, but this is not something that we have evidence of.

As stated in our response to consultation item 3, and in our response to the ICREL survey, there has been a definite increase in administrative costs and number of staff, with no increase in the number of trials opened. The CTU at Birmingham is also experiencing significant delays opening trials to recruitment which seems to be getting worse as time goes on rather than improving as might have been anticipated.

Other Examples for Consequences
DDO recognises that it may not be practical or necessary for tertiary assays to be conducted in accordance with Good Clinical Laboratory Practice (GCLP), particularly for early phase studies (Phase I & II) that the Drug Development Office conducts. These assays provide valuable insights into the mechanism of action of new/first in man anti-cancer agents and are often conducted by research scientists who do not have a regulatory compliant lab. These assays do not influence either patient safety or treatment but the information gained may support pre-clinical research development of new agents and thus benefit patients in the future. It would be unfortunate if such assays/labs were prevented for regulatory reasons from conducting this type or work.

Consultation Item No. 8
Adopting the text of the CTD in the form of a regulation could potentially achieve unity across the EU and do away with Member State specific variations, but in effect this would mean starting from scratch which could have significant resource implications for all stakeholders. In addition, it is not clear whether or not Member States are still able to implement country specific requirements in addition to the EU Regulations.

We would therefore welcome the proposal of reviewing the CTD and clarity on its provisions rather than re-issuing the Directive as a regulation as the former would leave more room for interpretation for practical use.

In particular we would welcome clarity on the following provisions:

1. Reporting to Eudravigilance when the Sponsor has UK only trials but business partners are conducting trials in the EU or worldwide.

2. Further guidance for notifying Substantial Amendments for either approval/notification and to which body (NCA and/or REC) would be welcomed.

With respect to Annual Safety Reports (ASRs) review or non-review by RECs, we believe that this would have little impact on reducing administrative burden for Sponsors.

We would welcome exploring the possibility of certain sets of accompanying guidelines becoming regulations, as we believe that there could be increased harmonisation if this was implemented.

We feel that introducing regulation would result in no obvious benefit for trials running solely in the UK, and could actually increase bureaucracy in certain MS rather than reduce it.

Key Issue No. 3: Regulatory Framework Not Always Adapted to the Particular Requirements
Consultation Item No. 9
The consultation recognises that the actual risk to a trial participant depends on a wide range of factors, and we feel that the Directive does not acknowledge these stratifications of risk, or make allowances for non-commercial Sponsors who have no involvement in the manufacture or distribution of IMPs. We have given some examples provided by the ICR below of how this affects us in practice:

Example 1
A large proportion of our trials test IMPs used within their marketing authorisation, against IMPs that are licensed but not in the precise setting being tested. The IMPs do not require particular manufacture or packaging, with supplies commonly coming from hospital stock and, in some cases, dispensed from community pharmacies. Despite this, in the CTD Annex 13 labelling is required together with detailed accountability records and even destruction logs, which is often impractical and places an unnecessary administrative burden on the participating sites and the Sponsor without improving patient safety.

TNT study: this study aims to see if the intravenous (i.v) chemotherapeutic agent carboplatin can delay disease progression compared with docetaxel (also an i.v. drug), which is the widely used standard of care. Docetaxel is used within its licensed indication. Carboplatin is used to treat lung and ovarian cancer, and has also been widely used to treat metastatic breast cancer outside the clinical trial setting for years. When used in exactly the same way within TNT, there is a theoretical requirement for annex 13 labelling. However, whether annex 13 labelling is actually required for an i.v. drug which is administered within a hospital and that the patient never handles is still disputed, and there is a lack of clarity from the regulator on this issue. Accountability logs and destruction logs are required for both drugs, though we cannot envisage a scenario in which either drug would be destroyed. Therefore the keeping of destruction logs in this instance seems an unnecessary burden to sites, and to the Sponsor in terms of oversight.

POETIC study: in this perioperative study, sites can choose whether to use one of two very similar drugs, anastrozole or letrozole. Both drugs are licensed for use after surgery for breast cancer, both are normally dispensed from community pharmacies, both are routinely prescribed for anything up to five years and this is what all patients in the trial will ultimately be prescribed. Trial treatment is for four weeks starting two weeks before surgery, and the control treatment is no perioperative IMP. Letrozole happens to be licensed for use neo-adjuvantly (i.e. as a treatment prior to surgery); anastrozole is not. Letrozole does not therefore need annex 13 labelling, but anastrozole, with its identical safety profile, does. Annex 13 labelling is required when dispensed by the hospital pharmacist, but is waived for community dispensing. However accountability requirements remain for community dispensing, although such an arrangement is impractical and there is lack of guidance on how this can be achieved. This places an unnecessary burden on participating sites, and the Sponsor in terms of audit, and protects neither the patients nor the research.

How should this be addressed?

• IMPs that are not physically handed to the patient to administer themselves should not require any specific labelling if used according to a recognised dose and schedule.
• Accountability and destruction logs should only be required for IMPs that require annex 13 labelling, and where they are dispensed from hospital pharmacies from stock specifically supplied for use in the clinical trial.

Example 2
SAE reporting places an enormous burden on large multicentre trials, particularly of cancer treatments, where often very sick patients may be being treated with highly toxic drugs. For trials in metastatic disease, SAEs are often confounded by events that are related to the fact that people are in the trial because they are dying of cancer, rather than any reaction to the IMP. Whilst the protocol excludes reporting of events directly relating to progression, caution on behalf of investigators results in many reports where the link to the IMP is possible but unlikely and which transpire to be disease related and thus would not have constituted SAEs had the reporting timelines been more flexible to allow clarification of causality before reporting.

In trials testing chemotherapy drugs, which are already known to be toxic and therefore cause serious adverse reactions (SARs), it has become routine practice for protocols to exclude commonly occurring SARs from immediate reporting. This strategy helps to ensure that genuine safety concerns are not lost in a deluge of inevitable SARs, which are a fact of life within chemotherapy treatment trials, whilst regular oversight provided by an Independent Data Monitoring Committee ensures event rates are closely monitored. This strategy does, however, require other systems to be put in place in order to provide the information for MHRA annual line listings that are a requirement of the EU CTD. The information provided to the MHRA is exactly as expected if you give thousands of people chemotherapy drugs. It is unclear what this information is used for. For example:

TACT2: this study has a 2x2 factorial design and tests four different combinations of chemotherapy treatment. One experimental treatment aims to maintain efficacy but reduce side effects, the other aims to improve efficacy. The IMPs used as control treatment are cyclophosphamide, methotrexate, 5 FU, and epirubicin. All are licensed for use in breast cancer, and all have been very widely used worldwide for many years. SARs in patients exposed to these drugs are well known, and the drug profiles will not be refined by any SAR data emerging from this trial that included a total of 4391 breast cancer patients. Despite this, annual line listings of all SARs were required. Overall, 1162 events were reported to the MHRA, only 27 of which were SUSARs. None of this information is of scientific interest; in fact it is difficult to imagine what useful purpose it could serve. Moreover, within the trial a far more informative dataset on the toxicity of the treatment regimens was collected in order to provide a clinically meaningful comparison between the drugs used in the control arm, and the drugs used in the experimental arms. In effect, two pharmacovigilance exercises had to be carried out, one for the purposes of the trial, the other to meet the demands of the EU CTD.

How should this be addressed?
• Individual SARs related to the use of IMPs that do not require annex 13 labelling should not require reporting to the MHRA (assuming that annex 13 labelling is as suggested in example 1 above). Recognition should be given to the role already played by the Independent Data Monitoring Committee and its review of aggregate data to highlight where rates of particular SARs are outside clinical expectations.

Example 3
Any trial closure prior to the scheduled end date needs to be reported to the competent authority more quickly than those that end as planned. There is no distinction between trials closed for safety reasons, and those that close for other reasons e.g. failure to recruit participants. Early reporting should be limited to trials that close for safety reasons. A 'final report' is required one year after the study has ended. In cancer studies, particularly those of short term adjuvant treatment in patients with good prognosis tumours (e.g. chemotherapy for early breast cancer), the study ends for the purposes of the EU CTD 30 days after the study treatment ends. One year on from this date there is

usually nothing of clinical relevance to report, because any results will take several years to emerge in this patient population.

How should this be addressed?
• We feel it would make more sense to request the outcome data for the main trial endpoints, whenever these are available, rather than providing an update one year after study treatment ends.

Example 4
The use of Non-Investigational Medicinal Products (NIMPs) in IMP trials as described in the "Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials", especially where NIMPs are used within their Marketing Authorisation (MA). For products used within their MA other systems are in place to protect patient safety that should be referred to instead, such as the "EC Compilation of community procedures on inspections and exchange of information with regards to handling of reports of suspected quality defects in medicinal products and the procedure for handling rapid alerts and recalls arising from Quality Defects".

Example 5
Definition of IMPs:

a. In academic paediatric trials it is not clear what should be considered as an IMP as most medication does not have an MA for use in paediatrics although they may have been used as standard treatment in paediatric medicine for a very long time.

b. Standard therapies used within their MA and as an active comparator in a clinical trial have to be considered as an IMP, but the purpose of the trial is not to gain further information about the authorised form of the comparator product but simply to compare this "control" treatment against the novel "research" treatment. Collecting additional safety data on the comparator can surely have little effect on the safety profile of these products.

The correct management of IMPs (labelling, accountability and destruction) within hospital pharmacies is extremely time-consuming. It is therefore imperative that only those products which actually meet the definition of an IMP are included in CTA applications, guidance from NCAs must therefore be appropriate and consistent, which is not the case at present.

The examples given above are far from unique, and we feel they clearly demonstrate that any theoretical protection that the EU CTD offers the patient is heavily outweighed by onerous record keeping and accountability of unproven value in trials that do not involve novel agents.

We would therefore welcome guidance for risk differentiation, ideally with onus on the Sponsor to justify the assessment. Based on the stage of clinical development and the body of data available for an agent we would support the possibility to consider a risk-based approach to certain CTD requirements but this should be on a trial specific basis with the onus on the Sponsor to justify rather than a 'broad brush' approach for later phase or certain studies. DDO only sponsor early phase oncology trials – therefore potentially higher risk trials and most often with novel drugs. However, there are risk differentiations even within these early phase studies. We would suggest that a risk based approach should take into account:

- The facilities where the trials are conducted (i.e. within specialist clinical units)
- The numbers of patients to be treated and the intensity and level of clinical monitoring of patients recruited to studies. (Patients on First Time in Man (FTIM) trials will be very closely monitored during and after treatment, but a comparable level of monitoring is unlikely on a larger Phase III/IV study and may not be needed)

Finally, it is acknowledged that EU guidance to support FTIM studies has been generated. Harmonisation in the application of these guidelines at the trial authorisation stage and a standardised application procedure for such studies would be welcomed.

Consultation Item No. 10
DDO's experience of smaller early phase trials has been that it has not been difficult to have a single Sponsor for UK-only trials and that the concept of a Sponsor is one that we have welcomed. 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 safety in multiple sites.

However, experience from CTUs is that the concept of a Sponsor acting as an EU legal representative has been open to varying interpretations, and therefore has led to reluctance to set up multi-national trials. We would seek clarification of this role in any revision of the CTD.

Consultation Item No. 11
Looking to the future of the clinical trials environment in the UK, we do not support a two-standard approach for commercial vs. non-commercial/academic Sponsors. When a trial is conducted the future use or potential use of the data may be unknown therefore all data generated should be of a comparable quality.

From a DDO perspective, with our experience in relatively small early phase trials we have no major issues with the current requirements for SUSAR and safety reporting. However, we understand that from an investigator perspective, particularly in relation to the large later phase studies, the issue of the large numbers of SUSARs circulated to all investigators on a study is a significant one. We would suggest that options to reduce this overload of SUSAR information for investigators involved in larger later phase studies needs to be considered within the context of the CTD. Our recommendation would be that a Sponsor should decide and document which SAE reports will be forwarded to trial investigators. This could be decided prior to the trial and documented in the protocol. This would limit the huge numbers of SUSARs being reported to trial investigators in large scale trials.

We feel there is no clear benefit to revising the content of the CTA Application. We would however suggest that the following modifications:

- That the "Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials" be revised.
- The reporting requirements for NIMPs should be revised, clarification should be provided as to when a product should be considered an IMP, and reference should be made to other guidelines for safety reporting for NIMPS e.g. Community Guidelines. The resource implications for academic sponsors of collecting and assessing safety data for IMPs are substantial without the added complication of trying to make these assessments for NIMPs.
- Active comparator is by definition an IMP. Defining IMPs in trials comparing product A to B is straight forward. However there is still confusion over what constitutes an IMP in complicated academic studies comparing multiple compounds e.g. ABC vs. ABD. Some NCAs advise that all of the compounds are IMPs while others state that only compounds C and D are IMPs. The guidance needs to include specific examples of this type to help NCAs and researchers define IMPs.
- A risk based approach to the implementation of the Clinical Trials Directive should be incorporated into all aspects of the guidance documentation.

Consultation Item No. 12

In addition to our response to Consultation Item No.11, as mentioned previously, one barrier to multinational research in the academic community is the requirement of a single international sponsor. To address this issue perhaps the definition of sponsor could be modified slightly for example to allow for:

1. a ‘co-sponsorship’ model; and/or
2. Member State specific versions of an academic trial which are sponsored on a national level (and thus exist as separate entities) but for which meta-analysis of the data is specified within the protocol; and/or
3. national sponsorship in individual countries with one named nominated sponsor retaining oversight of a trial without any legal responsibility.

It is extremely difficult to describe and quantify the impact of any such modifications.

Consultation Item No. 13

It is important to note here the difference between the various types of trials conducted. For example, many of the studies we support via the DDO have biological endpoints, and improving our standards around GCLP has definitely increased the validity and reproducibility of our data. However, these same standards have led to it becoming extremely difficult in some trials we support to introduce innovative readouts driven by observations as a trial proceeds. The consequence is that investigators specify only relatively standard assays and much potential information is lost because the system is too inflexible. If you notice a phenomenon that should be investigated with a different sample during the course of a trial there is a powerful incentive to ignore it, because to amend the protocol to allow the sample to be taken will stop the study for about 2 months or more. This issue needs to be addressed, as it is hampering the development of certain types of trials.

Many academics have indicated that the DDX system was less costly and bureaucratic, and that many large academic trials were conducted under this system that led to standards of care that define our treatment of cancer. The assumption is that the national rules will not fully revert back to how they were pre-Clinical Trials Directive. In the worst case scenario, academic trials may become hindered in multiple ways: the national rules may turn out to be cumbersome, possibly more so than is currently the case; countries may have national rules that make it impossible to conduct multinational trials; and there will be no oversight of how trials are regulated across Member States. This could limit progress of clinical research, especially in rare disease sites and paediatric trials.

However, we feel that given the current environment for clinical trials in the UK, the preferred option would be clearer guidance and more efficient implementation of the existing Directive via a risk-based approach.

Key Issue No. 4: Adaptation to Peculiarities in Trial Participants and Trial Design
Consultation Item No. 14

Experience from the CTU in Birmingham is that the definition of an IMP constitutes a major problem to the academic paediatric community as the majority of medicinal products do not have a MA for use in children despite having been used as standard care for many years. IMP management therefore creates a huge burden for academic sponsors of paediatric trials and participating sites. We would welcome the inclusion of a proviso within the Clinical Trials Directive, or provision of a guidance document, which recognises this fact and allows for alternative labelling and IMP management procedures for medicinal products being used in this context.

The majority of paediatric trials are multinational. Hence addressing the issues previously highlighted for academically sponsored multinational trials is essential if the intent is to promote clinical research for paediatric medicines.

Promotion of better sharing of information across networks is important and welcomed, to ensure that the correct studies are being performed and that duplication is minimised.

Consultation Item No. 15

We do not have any evidence relating to this. However it is obvious that this issue must be addressed. It would therefore seem sensible to include one of the national solutions to this problem within the Clinical Trials Directive.

Key Issue No. 5: Ensuring Compliance with GCP in Clinical Trials Performed in Third Countries
Consultation Item No. 16

We have no specific experience of this, but broadly support the EU commitment to support fundamental human rights for all trial participants. The issue to be addressed would be that of Sponsorship of multi-national trials involving EU and non-EU member states.

We would seek further clarification on section 7.3.2 of the consultation, as it was unclear as to what was meant by self-regulation in this context.

Consultation Item No. 17

A suggestion from the CTU in Birmingham is to request the International Committee of Medical Journal Editors to expand their requirements as stated in "Clinical Trial Registration: A Statement from the International Committee of Medical Journal Editors" to include listing to what standards trials have been conducted and whether or not non-OECD 3rd countries were involved; this will encourage academic trials to be registered as well.

We hope you find our comments useful. We would be happy to provide any further information or a representative to give oral evidence as required. Please contact Emma Greenwood, Science Policy Researcher at Emma.Greenwood@cancer.org.uk or on 0207 061 8358.

Cancer Research UK
January 2010

Appendix 1

Our involvement with clinical trials

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 Advisory and Awards Committee (CTAAC), which currently funds more than 150 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 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 almost 25,000 (which equates to ~5% of all EU participants presented in Table 3 of the consultation document). 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 33,500 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.

Appendix 2

Implementation of the Directive in the UK

The Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK implemented the Clinical Trials Directive through 'The Medicines for Human Use (Clinical Trials) Regulations 2004' (SI 2004/1031), which came into force in the UK on 1st May 2004.

In addition, the Medicines for Human Use (Clinical Trials) Amendment Regulations (the Amendment Regulations) came into force on 29 August 2006. The Amendment Regulations principally implement Commission Directive 2005/28/EC (the Good Clinical Practice (GCP) Directive) by amending the Clinical Trials Regulations which implement the Clinical Trials Directive (CTD).

We are generally supportive of the way the CTD has been implemented into UK law and supportive of the legally established timeframes for review of amendments included by the MHRA in UK legislation. We are also supportive of the attempts to streamline processes with ethics committees – evidenced in the Memorandum of Understanding between MHRA, the Central Office for Research Ethics Committees and the Gene Therapy Advisory Committee. The MHRA widely consulted with stakeholders in the UK and continues to do so; we have an established professional relationship with them.

In addition to the work of the MHRA, the UK Clinical Research Collaboration has provided guidance for researchers conducting clinical trials in light of the changing regulatory landscape. Notable among these measures are:

- The establishment of the National Research Ethics Service (NRES) in 2007 to help streamline the way that the Research Ethics Committees (RECs) interact.
- In January 2008, the development of the Integrated Research Application System (IRAS) to create a single, standardised, online application form for permissions and approvals.
- Between April and June 2007 the Regulatory and Governance Advice Service was launched. This service aims to provide consistent and definitive regulatory advice, complementing that delivered at the local level and is jointly delivered by a number of supporting and policymaking bodies.

- A number of 'model agreements' have been created to assist in the negotiation of acceptable terms between the NHS/Health and Social Care and the Sponsor of a clinical trial in various scenarios.
- The creation of the Research Passport to streamline the system for issuing honorary research contracts to researchers who do not have a contractual relationship with the NHS/HSC.

However, even with these ongoing initiatives we continue to identify problems with interpretation of the CTD and its implementation in the UK. We have continued to assess the impact of the CTD, both through our role as a Sponsor via our DDO, and our role as a funder of trials and 8 Clinical Trials Units (CTUs) in the UK. Our findings have fed into our response to this consultation.

Appendix 3

Glossary

ASR: Annual Safety Report
CMC: Chemistry, Manufacturing and Control
CR-UK: Cancer Research UK
CTA: Clinical Trial Application
CTAAC: Clinical Trials Advisory and Awards Committee
CTD: Clinical Trials Directive
CTFG: Clinical Trials Facilitation Group
CTOF: Clinical and translational Operations Funding Directorate
CTU: Clinical Trial Unit
DDO: Drug Development Office
DDX: Doctors and Dentists Exemption
DH: Department of Health
EORTC: European Organisation for Research and Treatment of Cancer
FTIM: First Time in Man
GCLP: Good Clinical Laboratory Practice (not an official acronym, but used by most people but not the MHRA)
GCP: Good Clinical Practice
HMA: Heads of Medicines Agency
IB: Investigator Brochure
ICR: Institute of Cancer Research
ICREL: Impact on Clinical Research of European Legislation
IDMC: Independent Safety, Monitoring and Ethics Committees
IMP: Investigational Medicinal Product
IRAS: Integrated Research Application System
i.v.: Intravenous
MAA: Marketing Authorisation Application
MHRA: Medicines and Healthcare Regulatory Authority
MREC: Multi-Research Ethics Committees
MS: Member State
NCA: National Competent Authority
NCRN: National Cancer Research Network
NRES: National Research Ethics Service
PV: Pharmacovigilance
QP: Qualified Person
REC: Research Ethics Committee
SAE: Serious Adverse Events
SAR: Serious Adverse Reaction
SUSAR: Suspected Unexpected Serious Adverse Reaction

UKCRN: UK Clinical Research Network
VHP: Voluntary Harmonisation Procedure

[i] The impact of the 'Clinical Trials' directive on the cost and conduct of the non-commercial cancer trials in the UK. J Hearn and R Sullivan. European Journal of Cancer 43 (2007), 8-13. DOI: 10.1016/j.ejca.2006.09.016

[ii] McMahon AD, Conway DI, MacDonald TM, McInnes GT (2009). The Unintended Consequences of Clinical Trials Regulations. PLoS Med 6(11): e1000131. Doi: 10.1371/journal.pmed.1000131

[iii] In May 2005 the CTU in question employed 0.5 staff in central regulatory role, and in November 2009 they now employ 3.5 staff in a similar capacity.