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Current Perspective

The impact of the 'Clinical Trials' directive on the cost and conduct of non-commercial cancer trials in the UK ☆

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ABSTRACT

BACKGROUND: The UK Medicines for Human Use (Clinical Trials) Regulations 2004 implemented the European 'Clinical Trials' Directive (2001/20/EC) (EUCTD) into UK law and came into effect on 1st May 2004. In the period leading up to the implementation of the EUCTD in the UK there were serious concerns that it would have major cost implications for academic units running non-commercial clinical trials.

METHODS: Directors and senior staff in 8 Clinical Trials Units (CTUs) were contacted and invited to participate in the study; arrangements were made for face-to-face interviews and the units were sent a questionnaire in advance of the meeting. The questionnaire was divided into six sections covering their involvement in non-commercial cancer clinical trials, and their perceptions of the EUCTD and its impact on all stages of trial development and conduct. Detailed cost data were also collected.

FINDINGS: The findings from the questionnaire and interviews indicate that the EUCTD has 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 for experienced staff who were anxious about whether they were interpreting the Directive correctly. Moreover, the CTUs were unable or unwilling to open trials in non-UK centres because of the different interpretation of the EUCTD by member states.

INTERPRETATION: The EUCTD has both increased the cost and caused delay to non-commercial cancer clinical trials run by major public sector Clinical Trials Units in the UK. Staff have felt that they were working beyond capacity and were feeling demoralised in many CTUs. Finally, rather than harmonising and simplifying the regulatory environment, the Clinical Trials Directive has stopped many units from running trials in international centres. The UK has taken action to address some of the problems identified by this and other research, but problems remain.

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1. Introduction

The primary aim of the European 'Clinical Trials' Directive (2001/20/EC) (EUCTD) was to simplify and harmonise the regulation of clinical trials using medicinal products across Europe. The UK Medicines for Human Use (Clinical Trials) Regulations 2004 implemented this Directive into UK law and came into effect on 1st May 2004. A pre-implementation impact assessment had raised significant concerns both in the UK and across Europe about the potentially deleterious effect of this legislation on non-commercial clinical trials.[1] With substantial long-term experience and base-line metric data on UK non-commercial cancer trials, a post implementation study was conducted to assess the actual impact of the EUCTD.

2. Methods

Six National Cancer Research Institute (NCRI) Accredited Clinical Trials Units plus the Cancer Research UK Drug Development Office (DDO), and the Wales Cancer Trials Network (WCTN) (8 major trials units in total) were included in the study. At the time of the interviews the 6 NCRI Accredited CTUs were: Section of Clinical Trials, Institute of Cancer Research, Sutton, CR UK & University College London Cancer Trials Centre, London, Medical Research Council Clinical Trials Unit, London, Clinical Trials Research Unit, Leeds, CR UK Clinical Trials Unit, Birmingham, and the UK Childhood Cancer Study Group (UKCCSG), Leicester.

The Directors of the eight units were contacted and invited to participate in the study; arrangements were made for face-to-face interviews and the units were asked to complete a questionnaire in advance of the meeting (either Yes/No answers, or on a five point Likert scale, for example ranging from 'very good' to 'very poor'). The questionnaire was divided into six sections (see Box 1).

Box 1. Questionnaire categories

Section A: Involvement in Trials
Section B: Perceptions of the effect of the EUCTD, and the flow of information
Section C: Impact of the EUCTD on starting up a trial
Section D: Impact of the EUCTD on conducting a trial
Section E: Impact of the EUCTD on closing down a trial
Section F: Cost Assessment

The Directors and senior staff were interviewed jointly in each unit by one of the authors (JH) and asked to comment on the categorical responses to the questionnaire that they had completed in advance of the meeting. Detailed cost data were also collected. Further comments were noted in the comments boxes on the questionnaires.

3. Results

Of the 8 CTUs surveyed, 5 were involved in phase II-III* trials alone all including Investigational Medicinal Products (IMPs), (*known in industry as phase IV clinical trials, i.e. using IMPs with an existing marketing authority). One CTU was involved in first in man phase I/II trials alone, and 2 were involved in both phase I/II and phase II-III trials. All CTUs had conducted or participated in clinical trials prior to, and since the 1st May 2004, and all were involved in trials that had been open before 1st May and that had continued under the new regulatory regime. One CTU had not been involved in any new trials that had opened since 1st May 2004, primarily due to difficulties regarding identification of a trial Sponsor.

3.1. *Immediate impact of the EUCTD*

All 8 CTUs reported that the EUCTD had made non-commerical cancer clinical trials much more expensive, and all believed that it had made conducting trials more difficult (5 thought much more, 3 slightly more), in particular more time-consuming due to increased documentation. Three CTUs had been unable to open or participate in a trial because it was deemed to be too difficult or expensive to do so. Specifically, this had been due to difficulties regarding the identification and confirmation of the trial Sponsor.

Most CTUs felt that they were currently in a learning curve and believed that administration of the additional documentation would become easier in future years. However, they expressed anxiety about several key new areas that had yet to be undertaken, for example completing a new Clinical Trial Authorisation (CTA), preparing Annual Safety Reports and formally closing down trials.

3.2. *Views on guidance from MHRA, Research Funders and NCRN*

All CTUs had found at the time of this survey the quality of information from the Medicines and Healthcare Products Regulatory Agency of the Department of Health (MHRA) on the requirements of the EUCTD poor or very poor. Six out of the seven responders to the question on information from research funders found it to be satisfactory to very good. However, there were negative comments on the quality of information available from all sources (see box 2), but in particular comments specific to the MHRA (see box 3).

Box 2. General comments on the quality of information from MHRA, research funders and NCRN

- Too much reliance on chance hearing about critical issues.
- No single source for clarification.
- Workstream advice: difficult to assess if this was interpretation or guidance.
- Too little and much too late, despite endless requests for information long before May 2004.

Box 3. Specific comments on the quality of information from MHRA

- Inconsistency in advice given and difficulties often experienced in trying to have a dialogue with MHRA.
- Difficult to get definitive information on areas such as pharmacovigilance and labelling when using normal hospital pharmacy stock (dispensing information).
- Website leads you in circles back to guidance notes, but it is the **interpretation** of these that is the problem – not getting clear-cut answers even when telephone.
- MHRA were unable to give precise answers regarding what to include in the Annual Safety Report.
- Conflicting advice. Lack of clear answers, eg definition of 'end of trial'

3.3. *Impact of the EUCTD on starting up clinical trials*

The CTUs were asked whether the EUCTD had made starting up a trial more difficult in key areas, compared to the existing Research Governance Framework. The results showed that the processes required to establish a new trial were viewed as much more or slightly more difficult in the majority of cases (see Fig. 1). In particular, all seven CTUs that had planned starting up international trials viewed the EUCTD as a significant barrier to doing so.

The 2 CTUs involved in first-in-man phase I/II studies that provided answers to a sub-set of questions felt that the requirements for Investigational Medicinal Product Dossier (IMPD) and for the Investigators Brochure (IB) were much more time consuming. Both these CTUs felt that the requirement for GMP manufacture of products was more time-consuming; for the unit already operating to 'GMP-like" standards, the additional workload was the requirement for audit.

3.4. *Impact of the EUCTD on conducting clinical trials*

The new requirements for conducting a trial under EUCTD were viewed as more time-consuming than existing procedures under Research Governance in the majority of cases (see Fig. 2), particularly on pharmacovigilance.

3.5. *MHRA Inspections and notification of amendments*

Four of the 8 CTUs had undergone an MHRA inspection in the past 4 years (one statutory and three voluntary). Seven out of eight CTUs had had to liaise with the MHRA regarding amendments to ongoing trials in the past year.

The inspection process was viewed as a positive exercise for establishing Standard Operating Procedures (SOPs) and confirming systems with MHRA. However, all four CTUs commented on the delay in receiving the inspection Report and that the Reports were not comprehensive in some cases eg. compared to the notes made by one Unit Director on areas for improvement/updating, and made new suggestions that another Unit Director did not agree with and had yet to be fully resolved; two of the units that had undergone voluntary inspections were still awaiting final sign-off of the Reports from the MHRA at the time of interview (up to 18 months later). In contrast, the CTUs had been invoiced for payment immediately after the inspection.

Similar to the comments on the overall quality of information from MHRA (section 1), liaison with MHRA regarding the conduct of ongoing trials, including the process for the notification of amendments was viewed as an area of major difficulty (see Box 4). 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 need to be considered as a substantial amendment – this was felt to be time-consuming and cause unnecessary paperwork and delay.

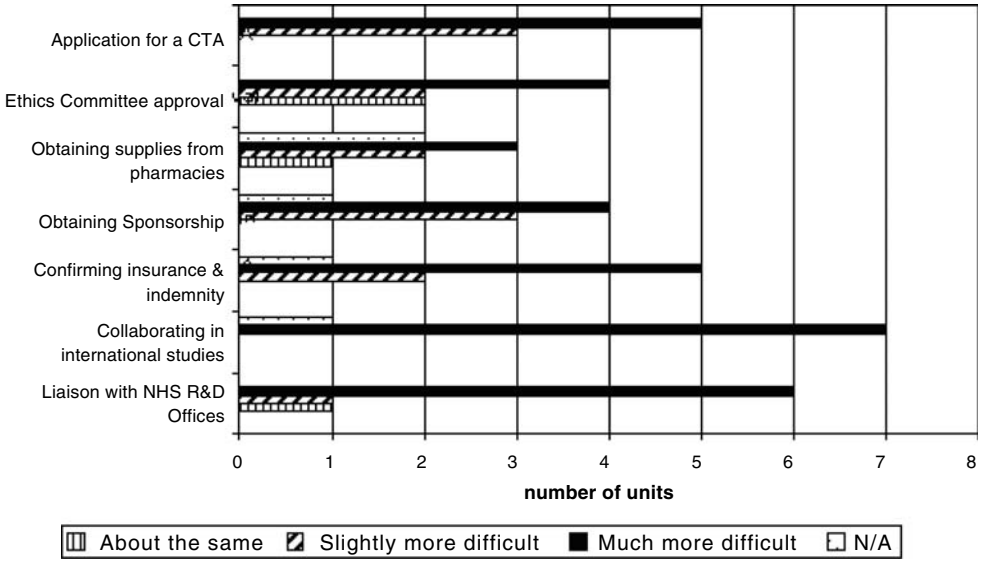

Fig. 1 – Impact on starting up a trial.

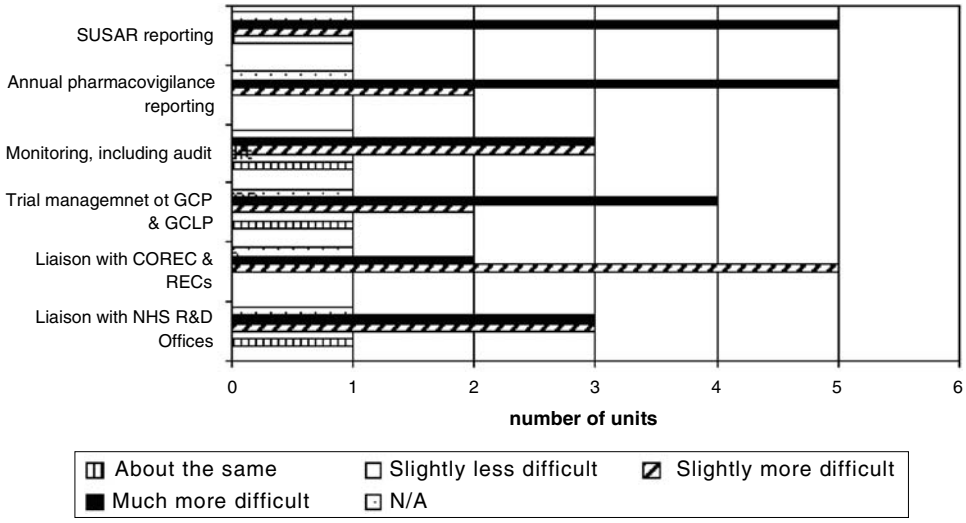

Fig. 2 – Impact on conducting a trial.

Box 4. Comments on liaison with the MHRA on ongoing trials

- Initially there was very little information available on how to make amendments, and now the MHRA either do not respond or the response is meaningless as does not state to which letter and/or trial that it refers to.
- Slow response, vague response not practical. Differing/conflicting advice eg MHRA guidelines on submission to ethics different to COREC.
- They [MHRA] are poorly resourced and as such they do take a while to answer questions. Also they are inconsistent with their answers (ie it depends on who you speak to on the day).
- At the end of 2004 there were lengthy delays in obtaining responses to amendments. Some amendments went missing and more than one response has been received for the same amendment.
- Amendments – too bureaucratic for small changes. Unclear what to go to MHRA and what Ethics. Problems just understanding the forms.

3.6. *Impact on closing down clinical trials*

Half of the units had been involved in a clinical trial that had closed since 1st May 2004. One unit felt that the process was helpful in defining the end of a trial. However, communication regarding one trial was not backed up in writing and caused considerable concern:

> "We needed to have additional patient information approved and the response from MHRA took a long time. Informal discussion with a member of MHRA before they left was very useful but we have nothing in writing from this discussion to present at any inspection. They reassured me that academic trials could take 2 years to meet the EUCTD but that has not helped the sleepless nights when staff worry about whether what they have done would be acceptable at inspection."

3.7. *Did trialists think that the EUCTD was justified in terms of improving the quality of trials, and of providing increased protection for patients?*

The units struggled to provide a general answer to these questions; they all felt that the EUCTD had not particularly improved the quality of the trials run by the CTUs which were already operating to the standards of the Medical Research Council Good Clinical Practice Guidelines, but some felt it may have improved the quality of trials run nationally outside their CTU.

The spread of answers reflects the dilemma of staff in answering these questions: 4 out of 8 units felt that the new regulations were justified in terms of improving the quality of cancer clinical trial, 4 did not. 5 out of 8 units did not feel that the new regulations had increased the protection of patients entering trials, 3 did.

With respect to the protection and safety of patients in clinical trials, most units felt that sufficient safeguards were already in place prior to the EUCTD with Independent Data Safety, Monitoring and Ethics Committees (IDMC) responsible for monitoring trials on a regular basis, and existing stringent review of Serious Adverse Events (SAEs) 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.

3.8. *Cost Assessment*

Of the seven units conducting phase II-III trials, two were able to provide direct comparisons of the overall costs of similar trials run in the unit before and after the introduction of the EUCTD.

Example 1 (*Comparison of two adjuvant breast cancer trials*). 'TACT' £171,713 pa, pre-EUCTD (A randomised trial of

standard anthracycline-based chemotherapy with fluorouracil, epirubicin and cyclophosphamide (FEC) or Epirubicin and CMF (Epi-CMF) vs FEC followed by sequential docetaxel as adjuvant treatment for women with early breast cancer in Breast Cancer)

'TACT2' £282,409 pa, post-EUCTD (Trial of Accelerated Adjuvant Chemotherapy With Capecitabine in Early Breast Cancer)

Example 2 (*Comparison of two adjuvant colorectal cancer trials*). 'FOCUS' £117,458 pa, pre-EUCTD (A randomised trial to assess the role of irinotecan and oxaliplatin in advanced colorectal cancer)

'COIN' £201,061 pa, post-EUCTD (A Phase III trial comparing either COntinuous chemotherapy plus cetuximab or INtermittent chemotherapy with standard continuous palliative combination chemotherapy with oxaliplatin and a fluoropyrimidine in first line treatment of metastatic colorectal cancer)

Further cost assessments were made of the CTU portfolios before and after the implementation of the EUCTD. 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, IB and 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 as being between £60,000 to £100,000 per trial. In addition to these costs, resources were needed to liaise with pharmacies regarding drug labelling and supply. Staff reported that the guidance on this topic were not very clear and one CTU reported that 4 staff had spent 150 hours collectively in trying to clarify what the drug labelling requirements actually were for the trials they were running. The costs associated with the need for additional administrative support and pharmacovigilance staff were estimated as approximately £50,000. IT programming and statistical input for SAE reporting was also needed but was not costed as a trial-specific activity by the CTUs.

In closing down a trial, two CTUs highlighted that there were costs associated with the requirements of archiving data. One unit reported that this cost was £3,000 per year for a 3,000 patient trial and that data was usually required for a minimum of 5 years, but was usually stored for around 15 years. A minimum of £15,000 per trial was anticipated as a direct cost for archiving.

4. Discussion

Despite the substantial amount of work undertaken by the Departments of Health, MHRA and the major public sector funders, including the Medical Research Council and Cancer Research UK, in particular to create the 'clinical trials toolkit' (www.ct-toolkit.ac.uk) this survey revealed that 11 months on from the start of the new regulatory environment substantial problems still remained. One of the most important issues was the 'risk aversion' that had pervaded these major CTUs. Confusion surrounding the interpretation and application of these new regulations was magnified by slow and multiple sources of guidance. In the absence of a single source of information there was a strong feeling of disillusionment and acute anxiety by experienced staff, which had inevitably led to over-interpretation of the guidance and 'regulatory creep'.

The delays to starting a trial introduced as a direct result of the EUCTD were estimated as between 6 and 12 months. The increased cost to units, excluding direct costs such as MHRA fees and ethics committee fees, was mainly the result of the additional staff resources required at every stage, from trial inception to closure. Every unit commented to this effect. The skills and expertise needed to meet the requirements of the Directive were in new areas, or areas for which more stringent reporting and accountability meant that existing staff felt that their skills did not match the new job roles. New posts in Quality Assurance, Pharmacovigilance, Information Technology, Contracts Officers and additional administrative support to handle large volumes of paperwork and archiving were identified as necessary. The doubling of costs found by this survey has been independently verified by a non-UK funder of non-commercial clinical trials, the European Organisation for the Research and Treatment of Cancer (EORTC).[2]

All but one of the CTUs that usually conducted or contributed to international studies reported that they had stopped opening trials in international centres because of uncertainty and anxiety regarding the regulatory requirements across Europe. Trials were being regulated on a Member State basis throughout Europe, making European-wide and international trials extremely difficult. Indeed rather than harmonising and simplifying the regulatory environment across Europe the EUCTD has had the opposite effect. Assessments of member state implementation indicates substantial differences in the legal interpretation and regulatory application of the EUCTD.[3]

Issues over identifying sponsors and delays with individual Trust R&D were closely associated. In the absence of a national template, standard Clinical Trial Agreements between host institution Sponsors and participating centres were being left to develop *ad hoc* agreements on a trial-by-trial basis. This had been a major stumbling block with, for example, one unit unable to open 10 new trials between 1st May 2004 and April 2005. There were major delays with individual R&D Offices seeking legal advice on each of the Agreements with over-interpretation of the Directive by lawyers, and furthermore multiple interpretations, all of which caused increased bureaucracy and delay.

Despite these problems the UK has at least been quick in its attempts to resolve the issue of the long-term support of publicly funded clinical trials. The MHRA has created a joint Good Clinical Practice (GCP) Consultation Committee with the public funders and, under the auspices of the UK Clinical Research Collaboration (UKCRC) Regulatory and Gover-

nance Workstream a number of initiatives have been set it motion – a single academic Clinical Trials Agreement, single source of help/guidance through a joint UKCRN/MHRA group, an MHRA inspection process designed to facilitate rather than fail, and the recent *Ad Hoc* review of Research Ethics Committee processes. More fundamental has been the wish articulated by the new Department of Health from England R&D strategy *Best Research for Best Health*[4] to overhaul the way Trust R&D offices work making them more pro-research and less bureaucratic. Thus many of the stakeholders particularly the MHRA have stepped up to the mark to deal with the issues highlighted by this survey. Finally some funders, such as Cancer Research UK, have given substantial additional money to individual CTUs to enable them to cope with the immediate impact of the EUCTD. In comparison to most EU member states the UK response has been excellent.[5]

However, major problems remain. International recruitment to many trials by most CTUs remains stagnant. The cost increase of running public sector clinical trials remains a real threat, particularly in areas of research without the support of a major funder. Regulatory creep remains a serious threat and there will need to be sustained audit and action to ensure that the mantra of 'fit for purpose' is really adhered to by both the public sector and regulators. Finally EUCTD-fatigue is leading to the very real danger that further malignant regulations will come out of Brussels. There is a need to ensure that the public funders across the EU work together to vaccinate fragile academic research from future regulatory threats.

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