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Re: Assessment of the Functioning of the "Clinical Trials Directive" 2001/20/EC. Public Consultation Paper.

Please find enclosed a response to this consultation paper, submitted on behalf of the University of Oxford and Oxford Radcliffe Hospitals NHS Trust (the Trust). As outlined within this paper, both organisations take on the role of Sponsor to clinical trials and the Trust spans three hospitals hosting clinical research.

Please address any queries to the undersigned.

Yours faithfully

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Assessment of the Functioning of the "Clinical Trials Directive" 2001/20/EC. Response on behalf of the University of Oxford and Oxford Radcliffe Hospitals NHS Trust.

Introduction

University of Oxford

The University undertakes the role of Sponsor to a huge amount of clinical research, of varied degree of risk, field, and indication. 552 research studies are currently active; of which 76 are clinical trials of medicinal products. Of these, 42 are being conducted within the United Kingdom. Ten trials units operate within the University.

Oxford Radcliffe Hospitals NHS Trust

The Oxford Radcliffe Hospitals NHS Trust (the Trust) is a highly active research organisation and hosts one of the NIHR Biomedical Research Centres. The Trust's Sponsored research activity amounts to 914 currently active research studies, of which 13 are clinical trials of investigational medicinal products. The clinical trial activity within the trust is, however, much greater than this, with 157 hosted trials (89 non-commercial sponsors; 68 commercial sponsors).

Clinical Trials in the EU

Consultation Item 1: Can you give examples of an improved protection? Are you aware of studies/data showing the benefits of the Clinical Trials Directive?

With reference to the intended purpose of the Directive, as outlined in this consultation paper, from the point of view of non-commercial research sponsors, we do not feel that it has achieved its overall purpose, as outlined below:

The protection of the health and safety of clinical trial participants;

With the advent of the Directive, non-commercial organisations were forced to look at the research that takes place within their organisation and assess their legal obligations in taking on responsibility as Sponsor for such research. The Medicines for Human Use (Clinical Trials) Regulations were the primary driver for this, but the Research Governance Framework for Health and Social Care has reinforced the need for provision of support and training for clinical researchers. Widely available training in Good Clinical Practice (GCP), and support in the submission of applications to ethics and regulatory authorities may have had an indirect, positive effect on the safety of trial participants, safeguarding subjects' interests through rigorous consent procedures; better trial safety and pharmacoviglance procedures; and a detailed focus on indemnity requirements from an organisational point of view. However, there is no hard evidence that this is so.

In the UK, there has been a reorganisation of funding provision, with the withdrawal of the 'Culyer' funding, to be replaced by National Institute of Health Research (NIHR). In order to enable this new funding stream to be administered, an entire new organisation has been set up, diverting resources from the actual research taking place.

Added to this is the resultant anxiety emerging amongst researchers that they may not be fully compliant with the Regulations. This anxiety is fed and exacerbated by the emergence of a range of expensive training courses, diverting researchers' attention from the safe and efficient conduct of their research to how they should prepare for and cope with a regulatory inspection.

The ethical soundness of the clinical trial;
One of the positive effects of the Directive in the UK has been the reorganisation of the national ethics service, streamlining the system and promoting a more rigorous and standardised review of applications, with the associated timelines for this. The improved quality of both regulatory and ethical review, assures investigators that their research has been considered to a high standard. There is an improvement in the quality of protocols from the outset, driven by the need to ensure that the sponsor responsibilities are covered and the desire to avoid the burden of amendments; less money is wasted on poor quality research.

The reliability and robustness of data generated in clinical trials
The requirement for trials to be monitored by the sponsor, along with mandatory regulatory inspection could, in theory, both protect participants and improve the reliability of the data. However, the impact of the burden and the costs incurred through these activities may well outweigh the benefits, as some potential sponsors may avoid taking on such responsibilities and, therefore, hinder research.

Simplification and harmonisation of the administrative provisions governing clinical trials in order to allow for cost-efficient clinical research.
The harmonization of procedures between member states, whilst being a very relevant aim, does not apply to many non-commercial trials, and the limited benefits of this are far outweighed by the administrative burden incurred in trials generally.

Key Issue 1: Multiple and Divergent Assessments of Clinical Trials

Consultation Item 2: Is this an accurate description of the situation? What is your appraisal of the situation?
Whilst the aim of the Directive was to harmonise procedures, the current system for applications in multi-national trials is time-consuming and adds an additional administrative burden, with the associated costs. Any alteration in favour of a more harmonised system would be welcome.

The consultation paper focuses on the problems around agreeing a harmonised protocol amongst Regulators, which are real but not the only issue by far. National laws add significant levels of bureaucracy and cost. For example, whilst the University holds insurance that covers its trials in all EU territories several territories require that specific insurance is taken out with a local provider. This is not easy to do (certainly first time around) and adds an often substantial fee to duplicate insurance cover, which is already in place. Some territories (notably Spain) require hospitals to use standard contracts when participating in trials, which usually do not allow the delegation of responsibilities to the hospitals. Under UK legislation such delegation needs to be recorded and, as a result, we do not know of any UK Sponsor which has managed to include Spain in a multi-national clinical trial. Harmonisation needs to

cover a broad range of issues if running multi-centre trials across Europe is the be simplified.

Consultation Item 3: Is this an accurate description? Can you quantify the impacts? Are there other examples of consequences?

Yes, all four weaknesses are accurate.
The European Organisation for Research and Treatment of Cancer (EORTC) also reported that trial initiation was 5 months slower (Hemminki and Lehtinen BMJ 2006)

Consultation Item 4: Can you give indications/quantifications/examples for the impact of each option? Which option is preferable? What practical/legal aspects would need to be considered in further detail?

Whilst an enforced system of cooperation between member states, with 'mutual recognition' of assessments made, has the potential to speed up the process of authorisations, it could also slow the process even further. Timelines would need to be protected without compromising the quality of review. Where one competent authority makes a decision on behalf of all member states, other states would have to accept the quality of decision making, presumably without the liability for that decision being taken by the lead state. Were such a system to be implemented, it would be essential that it be used for multi-national trials only. Otherwise, there could be exploitation of the arrangement, whereby a single trial could be reviewed by the competent authority with a reputation for less rigorous assessment. The possibility that rejected applications may subsequently be submitted to another member state would need to be covered in any such system.

Consultation Item 5: Can you give indications/quantifications/examples for the impact of each option? Which option is preferable? What practical/legal aspects would need to be considered in further detail?

One-stop shop for submission of assessment dossier
Within the UK, the system for submission using the IRAS form appears, in this early stage of implementation, to have the potential of achieving the aim of having a 'one-stop shop'. However, applying this principle on a EU wide basis, may incur the difficulties outlined above. Whilst ethics review results in an 'opinion' and the principles underlying the review are more universal, regulatory authorities give 'authorisation' carrying with it the legal liability for the decision.

Strengthening networks of national Ethics Committees involved in multinational clinical trials.
Allowing the possibility of "opting out", could lead to there being a two tier ethics review: firstly by the designated ethics committee within a specific member state; secondly where a member state does not accept the decision and opts for their own review. This scenario could easily lead to delays in the ultimate ethics decision.

Clarifying the respective scope of assessment of NCA and Ethics Committees
Increased clarity regarding the roles of NCAs and ethics committees would be helpful. This could avoid the scenario where an ethics committee requires specific changes to the documentation, which conflicts with the requirements of the NCA. Currently, resolution of such conflicts can cause delay to trial start.

Key Issue 2: Inconsistent Implementation of the Clinical Trials Directive

Consultation Item 6: Is this an accurate description of the situation? Can you give other examples?

Example 1: Substantial amendments

Legislation, and the requirements of the Directive regarding the definition of a Substantial Amendment is still, itself, open to interpretation. Not only are sponsors likely to err on the side of caution and define a change to the protocol as substantial, but some host organisations, wary of their responsibilities, are requiring sponsors to inform them of any amendment (whether substantial or otherwise), thus increasing the amount of bureaucracy and utilising resources for review of 'non-substantial' amendments that have no relevance to the safe conduct of a trial.

Example 2: Reporting of SUSARs

It may be that the increase in the number of SUSARs reported reflects an improved awareness of the definitions and reporting requirements of such events, rather than over-reporting.

As these requirements stand, such reports are submitted, having been unblinded. As such, they can only be reviewed as anecdotal reports, without the availability of blinded (placebo or comparator) data for comparison. Unblinding of one participant can lead to unblinding of the investigator teams.

One further point to make regarding SUSARs, is the form of reporting currently required. A few years ago, much anxiety was elicited by the requirement for electronic reporting of SUSARs through Eudravigilance. This was relatively easy to accomplish in the commercial sector, the resources being available for staff to undertake the highly expensive training for what would be, for such personnel, a frequent activity in their daily work. However, many academic and non-commercially sponsored trials involve a much lower risk associated with the IMP and the resultant SUSARs are an infrequent occurrence. This, coupled with a general lack of resources in the non-commercial sector, has meant that the required electronic reporting of SUSARs has never been achieved. In order to apply the same requirements for all sponsors, the systems, and software for reporting such events could be much simplified and, consequently, cheaper.

Example 3: Scope of the Clinical Trials Directive

Since the advent of the Directive and the Regulations in the UK, the classification of trials, particularly at the borderline between 'interventional' and 'observational' has been a challenge, both to researchers and those responsible for governance and compliance.

A protocol should be clear and unambiguous, which is sometimes not the case, but the outcome of using the EC algorithm appears to be very much dependent on the language or phraseology employed within the protocol rather than the underlying nature of the study.

Through its interpretation of the Directive the MHRA consider a trial to be interventional if a drug is given to a patient and assessments of its action are taken at baseline and at a time point following prescription of the drug, regardless of the fact

that the clinical decision for prescription of that drug has been taken and would be overseen completely independent of the study. The impact of this definition on the conduct of clinical research within the non-commercial sector is great. Such studies may not be able to proceed, due to a lack of the resources required to achieve compliance.

It is difficult to understand the difference between such a study and a post marketing surveillance study sponsored by industry, other than that the former has the objective of advancing scientific knowledge of the effects of the drug involved, with a potential to translate such knowledge into a change for the better in normal clinical care. The inclusion of additional (non-invasive) diagnostic or monitoring procedures would be unlikely, in such a case, to affect the risk involved in the study.

It should be noted that such instances arise through interpretation of the Directive. Were the definition of a trial within the scope of the Directive to be simplified and clarified, such errors could be avoided (See Item 13)

Consultation Item 7: Is this an accurate description of the situation? Can you quantify the impacts? Are there other examples of consequences?

Insufficient patient protection
The requirement for SUSARs to be reported in trials using low risk, licensed IMPs must lead to a marked increase in the number being reported. Where SUSARs are thus submitted in high numbers, this must have an adverse effect on the processing of this information through Eudravigilance, with the effect of diverting regulators' attention from those events that are of relevant concern. The removal of the requirement to submit SUSARs in trials using IMP where the safety profile is well known, would address this, and relieve the reporting burden, both at an investigator level and at that of the sponsoring and host organisations.

Increase of administrative costs
As outlined in the response to Consultation Item 1, the increase in administrative costs has had a profound effect on non-commercial sponsors, but this is not necessarily to the detriment of those sponsoring organisations. However, the increase in administrative costs has not been reflected in the funding support in the form of grants from the relevant research charities. Such an increase in costs, has been borne by the organisations themselves.

Consultation Item 8: Can you give indications/quantifications/examples for the impact of each option? Which option is preferable? What practical/legal aspects would need to be considered in further detail? In particular, are the divergent applications really a consequence of transposing national laws, or rather their concrete application on a case-by-case basis?

Reviewing the Clinical Trials Directive with a view to clarifying provisions, where necessary.
A review and amendment of the Directive would be welcome, providing the clarifications outlined in this paper and amending the scope, thereby rendering it less open to interpretation, both within and between member states.

Adopting the text of the Clinical Trials Directive in the form of a regulation.
Were the 2001 Directive to be repealed, it might make sense to include the 2005 directive and incorporate the two directives as one. Whilst repealing the Directive and replacing it with a regulation may avoid divergent interpretation between member states, without there being any amendment to that Directive, it would remain open to interpretation. Within the UK, it has been seen that the national interpretation has created many challenges in the non-commercial research world.

Key Issue 3: Regulatory framework not always adapted to the practical requirements.

The Directive has had a profound impact on non-commercial research and has introduced a level of bureaucracy that is, in some areas, unachievable. The 'broad-brush' approach fails to take into account the nature of academic research and has elicited a level of anxiety in researchers and host organisations that impedes the conduct of trials.

Consultation item 9: Can you give examples for an insufficient risk-differentiation? How should this be addressed?
Although the regulatory authorities in the UK have gone some way towards introducing an assessment of risk in their approach to compliance with the Regulations, there is still much to be achieved. Whilst some trials are conducted with a view to developing new compounds, many use licensed medicines, often within their licensed indication. The risk level of such trials is minimal. Where a high-risk patient population is involved, the use of low-risk medicinal products may have minimal, no effect, or be potentially beneficial for that population, from the point of view of safety. Examples of low risk IMP, used in non-commercial research are multivitamins in Alzheimer's Disease; aspirin and fish oil in heart disease.

Whilst it is possible to take an adaptive approach to insurance for low-risk trials in an organisation where the expertise are available to do so, not all such organisations have this knowledge and experience available and some will decline to take on Sponsor responsibilities in view of this. A creative approach can be applied to the matter of safety reporting requirements, for low-risk trials, with the protocol clearly stating which adverse event data will be collected but, again, experience and confidence is required to achieve this.

The labelling requirements of the IMP create many difficulties and add considerably to the financial burden of trial conduct. The UK regulators will agree to certain IMPs being dispensed according to normal clinical practice, but this is dependent on whether there is a marketing authorisation for that particular indication. In paediatrics, however, most drugs are not licensed for children and much expense must be borne by the sponsor to allow for the labelling requirements of such products, with no beneficial effect on the safety of participants.

Consultation item 10: Do you agree with this description? Can you give other examples?
This can be addressed through formal delegation of Sponsor responsibilities to organisations in other member states.

Consultation item 11: Can a revision of guidelines address this problem in a satisfactory way? Which guidelines would need revision, and in what sense, in order to address this problem?

A review of the guidelines, whilst welcome, would be insufficient to address the majority of the concerns of the non-commercial research community. A risk-based approach to all of these issues would be more appropriate. The rules for safety reporting; reporting of SUSARs; labelling of IMP; and the content of the clinical trial application could all be simplified if the existence of a marketing authorisation were to be taken into account.

Consultation item 12: In what areas would an amendment of the Clinical Trials Directive be required in order to address the issue? If this was addressed, can the impacts be described and quantified?

Most of the difficulties and deficiencies of the Directive were foreseen prior to its implementation as a regulatory framework in the UK. Non-commercial organisations and the regulatory authority have been forced to attempt to fit inappropriate regulations to academic research. A radical review is long overdue. It is essential that this review take into account the arena of non-commercially sponsored research and apply a risk-based approach to the scope, as outlined in the response below.

Consultation item n°13: Would you agree to this option and if so what would be the impact?

The proposed approach of excluding "academic/non-commercial" research from the scope of the Directive would not be acceptable. Whilst many of the studies conducted in Oxford involve licensed IMPs, some of the trials are Phase 1 trials of new vaccines, with orphan drug status, being developed within the University. Others are used to contribute to an application for marketing authorisation, by a pharmaceutical company. Much emphasis has recently been placed on the need for industry and academia to work together in collaboration and such strong and growing relationships would be adversely affected by such a move.

An alternative strategy could be explored, through a risk-based approach. Those trials using already licensed IMPs, for which the safety profile is well known, could be excluded. Such an amendment would address the issues of safety reporting as outlined previously.

An entirely new professional community has been created in response to the Directive, to enable organisations to protect themselves from non-compliance with the Regulations, along with costly courses to enable these professionals to gain the knowledge required to achieve this. Whilst this has had the positive effect of increased provision of support to researchers, were this change to be implemented, much of this support could be redirected to focus resources on the promotion of high quality research, through what is, after all, 'good clinical practice'. This would result in an environment where participant safety is protected to an optimum level.

Within this proposed review of the application of the Directive to non-commercial sponsors, there should be consideration of the costs and impact of regulatory inspections on these organisations. Inspections of NHS Trusts, currently focus, not

only on their responsibility as Sponsor, but also as a host organisation. Taking the Oxford Radcliffe Hospitals NHS Trust as an example, this means that the scope of an inspection takes in a range of 159 trials, rather than the 13 that would apply, were the inspection to focus solely on sponsor responsibilities.

An alternative option could be available for non-commercial organisations: rather than mandatory inspections by the regulatory authority, a system for reciprocal audit (peer review) could be arranged. This would have the added advantage of sharing of good practice and networking between organisations, with the result that systems would be harmonised, at least on a national basis. The costs of inspections could be diverted to the provision of good clinical care and, without the requirement for inspections of non-commercial organisations, the regulatory authorities would be able to focus their own resources on the regulation of medicines.

Key Issue 4: Adaptation to peculiarities in trial participants and trial design

Consultation item n°14: In terms of clinical trials regulation, what options could be considered in order to promote clinical research for paediatric medicines, while safeguarding the safety of the clinical trial participants?

The main problems experienced within paediatric research are the same as outlined for all clinical trials. The emphasis is on the quality of the paperwork, rather than the quality of the clinical procedures involving the participants. There is a lack of infrastructure in most centres to meet the bureaucratic and training requirements imposed by the Directive.

Consultation item n°15: Should this issue be addressed? What ways have been found in order to reconcile patient's rights and the peculiarities of emergency clinical trials? Which approach is favourable in view of past experiences?

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The UK is one of only 10 member states that have specific legislation to cover this. The principles surrounding trials in emergency situations should reflect those applied in normal clinical care, where treatment is administered according to the immediate needs of the patient. Where it is uncertain as to which treatment should be administered, and where informed consent is not possible, it would be appropriate and ethical to undertake some trial investigations (e.g. collection of additional blood samples); or to randomly allocate the treatment, obtaining subsequent consent when and if this becomes possible.

Key Issue 5: Ensuring compliance with Good Clinical Practices (GCP) in clinical trials performed in third countries

Consultation item n°16: Please comment? Do you have additional information, including quantitative information and data?

It is appropriate that research should be conducted in countries where the objectives are consistent with the populations to be studied. Much research conducted in third countries is conducted to a satisfactory standard with sufficient oversight and monitoring by the sponsoring organisations responsible. An important consideration should be to that of the local cultural differences in approach to issues such as informed consent and the expectations of the population.

Consultation item 17: What other options could be considered, taking into account the legal and practical limitations?

Ethical review is generally undertaken in individual third countries, at a local level. However, these reviews may not be as rigorous as those undertaken within the EU. This could be addressed by ensuring that trials conducted in third countries are reviewed by a 'flagged' ethics committee within the EU, as well as at a local level. The University of Oxford has a similar approach to this in review of its tropical medicines trials.

Consultation item 18: What other aspect would you like to highlight in view of ensuring the better regulation principles? Do you have additional comments? Are SME aspects already fully taken into account?

One of the major problems arising from the implementation of the Directive is that it appears to be aimed at commercial sponsors. Paragraph 2.3 of the consultation paper refers to the sponsor of trials, with no mention of academic and healthcare institutions. It is essential that these organizations are considered in any review of the Directive, with particular consideration being given to the suggestions for a risk based approach, as outlined in item number 13.

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