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REVISION OF THE 'CLINICAL TRIALS DIRECTIVE' 2001/20/EC

CONCEPT PAPER SUBMITTED FOR PUBLIC CONSULTATION

A RESPONSE

Respondent: Christopher Roy-Toole
Barrister
Member United Kingdom NHS Research Ethics Committee

Category of Respondent: Private Individual

Contact: c.roy-toole@btconnect.com

This is a response to the Concept Paper on the Revision of the Clinical Trials Directive 2001/20/EC. The Concept Paper seeks responses only on a limited range of issues arising from the 2009/10 Public Consultation. My response follows the order of the questions posed in the Concept Paper. My response is based at least in part upon my original submission to the European Commission in the 2009/10 Public Consultation, to which reference should be made where necessary[1]. Time constraints imposed upon me by organisational deadlines and limitations in access to research data have prevented me from substantiating my comments with as much empirical evidence as might be desired. My response therefore confines itself to legal and procedural issues surrounding research governance. The opinions stated herein are my own, unless otherwise cited, and are submitted in a private capacity. You may publish this document.

Foreword

The Concept Paper sets out some stimulating propositions. Taken as a whole, it is a positive step forward in the debate on the revision of the Directive. However, it is predicated on implicit assumptions that are wrong and which require fundamental re-evaluation.

The Concept Paper assumes that the review of the science and safety of the protocol, and specifically the assessment of the risks and benefits to the trial subjects, can be separated from the ethical review of the impact of the study on their rights, safety and wellbeing. This assumption leads the Commission to the conclusion that the role of the competent authority in the scientific review of the protocol is amenable to some type of centralised decision making which need not be applied to the process of ethical review[2]. In truth, the processes of ethical and scientific review cannot be separated and must at some stage be joined. The CIOMS Guidelines demonstrate this[3], but the Commission and elements within the research community appear to have overlooked it. Proponents of functional separation of the tasks conducted by competent authority and ethics committee believe that they are promoting rationalisation when in fact they exacerbate the duplication of those tasks. So if scientific review of the protocol must alternatively be centralised or 'regionalised', then the same approach must be applied to ethical review. The logical conclusion is that the two review processes must be carried out together and by a composite governance body established for that purpose[4]. In view of the reluctance displayed by the Commission to embrace the prospect of the assessment of ethics by a committee centralised at European level, the case is strengthened for the introduction of composite regulatory authorities in every member state to undertake the processes of scientific and ethical review within the same national organisational framework. This could do more to speed up processing times and improve the quality of decision making than anything proposed in the current Concept Paper. Special reference should be made to my consideration of Consultation Topic 1.3.

Consultation Topic 1: Cooperation in assessing and following up applications for clinical trials

Consultation Item 1:

Answer: No. Single submission will reduce administration but not greatly.

Consultation Item 2:

Answer: Yes. Single submission implies co-ordinated assessment.

Topic 1.1: Single Submission and Separate Assessment by National Competent Authorities

The submission of a single application for clinical trial authorisation through a central EU portal could reduce the administrative burden attendant upon setting up multi-national clinical trials by eliminating the need for multiple submissions. National competent authorities would be able to access a centrally submitted application dossier online, thereby enabling simultaneous access to information by all competent authorities involved in authorisation.

However, this would increase the technical and organisational burden on the entity responsible for administering the central portal. Technical or organisational errors in centralised processing might delay the application process. A question arises as to whether this additional technical burden upon central EU institutions is justified when measured against the administrative savings to the sponsors in the case of multi-national studies that are to be conducted in only a few member states.

The benefit of single submission would be negated by retaining the current arrangement of separate assessment at the level of the national competent authorities. There would be an additional question as to whether the material received from this central repository would be complete, and furthermore, would be *verifiable* as being complete. Additional audit and quality assurance measures would need to be put in place to ensure that protocols were not rejected on the basis of errors and omissions in centralised processing. A special problem is how central submission to a European agency could be harmonised with systems in individual member states that enable applications for research approval to be submitted at the same time to both national competent authority and national ethics committee. The IRAS system in the United Kingdom is an example of this type of system[5].

When such information is shared between central and national repositories, there arises a curious legal question as to which entity would assume legal liability for errors in transcription and transmission of information relating to applications for clinical trials authorisation and for errors in the resulting decisions.

Topic 1.2: Single submission with subsequent central assessment

Consultation Item 3:

Answer: Yes but with qualification [see my Foreword and Item 5].

Scientific review cannot be separated from ethical review[6]. The ambiguous nature of the wording of the Clinical Trials Directive 2001/20/EC permits the function of scientific review of the risks and benefits of a clinical trial to be allocated either to the ethics committee, or to the competent authority, or to both[7]. Issues relating to insurance, indemnity and compensation can be allocated specifically to the competent authority[8]. But the ethics committee has an inalienable legal duty to consider whether the assessment of risks and benefits, whether assessed by itself or by the competent authority, is justified[9].The Clinical Trials Directive also makes a clear provision for an ethics committee to be an independent body in a member state[10]. Central assessment of the risks and benefits of the protocol of a multi-national clinical trial is not permissible, on the current state of European law, without reference to a national ethics committee for approval[11]. Therefore centralised assessment of both the scientific merit and the ethics of a multi-national clinical trial cannot be undertaken on the current state of the Directive.

Topic 1.3: Single submission with Co-ordinated Assessment Procedure [CAP]

Consultation Item 4:

Answer: Yes.

Consultation Item 5:

Answer: No. The categories are incorrect.

CAP is not workable in its proposed form. This is because the three-way classification that the Commission has adopted[12] for the separation of scientific issues from ethical and local issues is flawed in logic and in law. CIOMS guidance states that ethical review cannot be separated from scientific review. CIOMS Guidelines also defines the components of ethical and scientific review as follows;

> Scientific review must consider, *inter alia*, the study design, including the provisions for avoiding or minimizing risk and for monitoring safety. Committees competent to review and approve scientific aspects of research proposals must be multidisciplinary.
>
> If the ethical review committee finds a research proposal scientifically sound, or verifies that a competent expert body has found it so, *it should then consider* [*my italics*] whether any known or possible risks to the subjects are justified by the expected benefits, direct or indirect, and whether the proposed research methods will minimize harm and maximize benefit.[13]

The CIOMS Guidelines state that the assessment of the risks and benefits to the trial subjects is a separate question to the scientific review of study design, risk minimisation and safety monitoring. The CIOMS Guidelines state that the review of risk and benefits falls to the ethics committee to perform. This means that the assessment of the risks and benefits must fall within category (b) of the Commission's tripartite schema for the application of CAP. This is consonant with the wording of the Directive, which states that it falls to the ethics committee to consider whether the risks/benefit assessment that has been made, either by themselves or by another prior body, is justified[14].

It cannot properly be said that any assessment of the risks and benefits to the trial subjects is complete without a consideration of the suitability of the site and the competence of the researchers who will conduct the study, as these factors also impact upon safety. Moreover, the Commission should accept the reasoning that the assessment of the risks, benefit and inconvenience of the trial subject should also embrace an assessment of the protection that the study affords to their legal rights[15]. This logic also serves to bring the risk/benefit assessment firmly into category (c) of the Commission's schema.

The Commission's three-way classification of scientific, ethical and local issues is therefore shown to be an error. If CAP were to proceed upon a proper basis, then the best that could be hoped for is that it might provide some advance warning to sponsors as to whether their studies are likely to be given further consideration by national competent authorities in more than one member state *from the standpoint of scientific methodology alone*. The risk/benefit assessment would be determined finally by the national ethics committee.

So the real question for the Commission is whether CAP is worth the time and the expense to achieve these limited objectives. Do the category errors that beset this model for CAP also apply in the same way to the VHP pilot scheme? And if they do, would the Commission be better advised to abandon plans for separation of scientific and ethical review by means of coordinated assessment? The Commission should focus instead on reducing delays and inconsistencies in research governance by bringing scientific review and ethical review within the function of a composite single regulator for clinical trials in every European member state. This would reduce the need for multiple submissions to separate committees and reduce the number of 'critical control points' in research governance from which inconsistent decisions might arise. The Commission should be mindful that the Government of the United Kingdom is evaluating the principle of a single regulator at this present time[16]. If the Commission were to hold a separate consultation on that issue, it might find more support for the idea than it first supposed.

Topic 1.3.2: Disagreement with the assessment report

Consultation Item 6:

Answer: Opt-Out is the only option.

The Commission proposes three alternative mechanisms to resolve dissent amongst national competent authorities on the recommendations of a CAP assessment report. These mechanisms are; an opt-out on the basis of 'serious risk to public health or to the safety of the participant', voting on a specified majority and dispute resolution by a central body appointed for that purpose. Comparison can be made to the dispute resolution scheme available to national regulatory authorities under the decentralised[17] and mutual recognition procedures[18] for the grant of marketing authorisations. In the event that another member state cannot accept the assessment report prepared by another member state on the matter of the grant of marketing authorisation, it is possible to make a reference to the Committee for Medicinal Products for Human Use [CHMP] for arbitration[19]. The Commission affirms the results of the arbitration and the decision binds the national competent authorities in member states. The question is whether a similar arbitration procedure should bind the hands of dissenting national competent authorities in a dispute over a clinical trial authorisation in their own member states. There are a number of issues that must be stated at the outset.

Firstly, there is no institution of the European Union that exists for this purpose and so one would have to be created or designated for that purpose. If the European Medicines Agency were to be designated to that role it would raise concerns as to the proper separation of function between agencies responsible for the authorisation of trials and the approval of licensing for marketed drugs so as to ensure impartiality from adverse influence emanating from the pharmaceutical and academic research sectors.

Furthermore, the national ethics committees have the last word on the matter of the protection of the subject and the public. Even if the national competent authority were bound to accept an arbitrated decision on clinical trial authorisation, that decision would not bind the ethics committee, which is free to reconsider all matters relating to the risk/benefit assessment. Any binding procedure introduced under CAP, and which was directed to the ethics committees, would strike at the core requirement of the Clinical Trials Directive that they should be 'an independent body in a member state'[20]. If there ever were to be composite regulatory authorities in member states, comprising the functions of scientific and ethical review, then this power would need to be 'ring-fenced' from central interference if the European Commission is to remain committed to the notion that ethics are best determined by the member states in which it is to be applied.

Then there is the matter of public policy. The pharmaceutical legislation of the European Union is concerned not only with the safety of the public but also with the need to maintain the free movement of goods and services within the European Economic Area. Applications for marketing authorisation are procedures that concern the interplay between the private law rights of the sponsors who apply to market their product in the European Union and the public law concerns of national regulatory authorities who must ensure safety in pharmaceutical applications. In the case of applications for clinical trial authorisation, this interplay between private law and public law concerns is different. Clinical trial authorisation primarily engages the public law duty of competent authorities to safeguard the nation's health. The commercialisation of the sponsor's intellectual property rights in the trialled drug do not weigh heavily in this balance. Safeguarding the public health should be carried out on a precautionary basis. The safest way for a competent authority to apply the precautionary principle is to refuse the application for clinical trial authorisation. Subsidiarity dictates that the national competent authority is best placed to make this decision as it affects the citizens in its own member state. In the context of CAP, this means allowing the national competent authority an unfettered power to opt out of the group decision.

If public policy reasons dictate that national competent authorities should not be fettered in their discretion to refuse an application for clinical trial authorisation of an investigational drug to be used within a member state, in circumstances where there are substantial concerns about the public safety, then the use of arbitration procedures within CAP is likely to be a non-starter. The Commission should seek and publish expert legal opinion on this matter.

A similar reasoning applies to any proposal for voting by majority to resolve disagreements over assessment reports submitted under CAP. If an arbitral decision cannot bind the dissenting party in those circumstances, then on what basis of law or policy should a national competent authority be bound merely by a show of hands in a majority vote?

Topic 1.3.3: Mandatory or Optional Use of CAP?

Consultation Item 7:

Answer: Optional use only.

If the analysis under Consultation Item 6 is correct, and if public policy forbids the binding of a national competent authority on the matter of an authorisation of a clinical trial within its own state, then CAP can never be anything other than an optional process. As such, what is the advantage of CAP over the current VHP pilot scheme?

Additional Question: Is CAP applicable to large scale MNCTs?

The Co-ordinated Assessment Procedure [CAP] has a resemblance to the current arrangements for the Voluntary Harmonisation Procedure [VHP][21]. The current VHP pilot is limited to multi-national clinical trials taking place in no less than three member states. The Concept Paper does not specify whether the CAP is intended to apply to all multi-national clinical trials [MNCTs] involving two or more member states and whether it is expected to be equally applicable to authorisations of large scale studies involving five or more member states. A question arises as to whether CAP is the appropriate model for higher powered studies involving a larger number of member states.

The Commission has set its face against the centralised assessment of applications for clinical trial authorisation by means of a scientific committee made up of representatives of all the European member states, and has given its reasons[22]. But if there is a need to

run larger and better powered clinical trials involving rare diseases, and if the paucity of studies of this type can be attributed at least in part to the administrative difficulties involved in obtaining authorisation from separate national competent authorities, then the size and number of such studies might be boosted by the introduction of centralised assessment. In order to bind national competent authorities by the decision of a superior central body constituted for that purpose, primary legislation would be required and in the form of a European Regulation.

Would the European Research Area vision be assisted by such a scheme? Or would the difficulties in separating scientific review from ethical review militate against its use?

Topic 1.3.4: Tacit approval and timelines

Consultation Item 8:

Answer: It depends on how fast national ethics committees already are.

Reducing timelines for presumed low risk studies of the proposed 'Type A', whether submitted under CAP or under the national procedures, will depend upon the degree of cooperation that presently exists between national/local ethics committees and national competent authorities in the sharing of information between them that is referent to the approval of a clinical trial.

The United Kingdom operates the IRAS system that provides a single portal for the submission of all applications for clinical trial authorisation and ethics committee approval. Other member states will no doubt operate other systems. A feasibility study should determine if IRAS could provide a template for submission systems in other member states in order to meet these proposed timelines.

Processing of 'Type A' studies within a national research governance system would also require a sort of triage system to prioritise low risk from higher risk studies. The Commission should be wary about imposing arbitrary classifications upon research studies that ascribes to them a presumed risk based on general characteristics. Who decides the risk profile for allocation of studies to 'Type A'? How long would it take to decide that a study is sufficiently low risk to be allocated to a decisional fast-track? How does one guard against the risk that governance bodies become 'normalised' to risk?[23] Should ethics committees be left to make up their own mind about the level of risk and try to set their own internal deadlines for processing applications rather than have them imposed from above?

It should be noted that the UK National Research Ethics Service now operate a proportionate review service for studies that may present no material ethics issues for deliberation[24]. But clinical trials are excluded from this fast-track procedure. Despite this, recent evidence suggests that timescales from application to ethical approval is not a rate-limiting step in the United Kingdom and that the average turnaround time is around 35 days[25]. On the strength of the UK example, why is it necessary for a national research governance system to be subjected to targets for turnaround set by external European bodies if internal quality assurance measures can achieve a comparable result?

Consultation Topic 2: Better adaptation to practical requirements and a risk-adapted approach to the procedural aspects of clinical trials

Topic 2.1: Limiting the scope of the Clinical Trials Directive

Consultation Item 9:

Answer: No comment. I await evidence from researchers and regulators.

Consultation Item 10:

Answer: Yes. Non-commercial sponsors should not be excluded.

Academic researchers should not be excluded from the scope of the Directive. They are not immune from error and the patient requires protection from such errors as much as from those committed by their commercial counterparts. The real question is whether the current division of clinical trials into ‘commercial’ and ‘non-commercial’ categories is one that should be abolished as serving no benefit to the patient, the researcher or to the wider public interest.

What is unclear from a reading of the Directive is why this division exists at all. Is it to guard against fraud in the promulgation of research with commercial benefit to the sponsor? If it can be said that the need to safeguard against fraud or research misconduct is the same no matter whether the clinical trial be commercial or non-commercial, and that the only issue is the risk of misconduct within a particular study or field of studies, then it begs the question as to what is the value in retaining the distinction between commercial and non-commercial drug trials in the first instance. Every study should be subject to governance arrangements that enable fraud or

misconduct to be detected irrespective of the fact that data use is involved in support of a marketing authorisation. The only remaining justification for retaining the distinction between commercial and non-commercial studies might lie in a greater risk to public safety associated with the marketing of new drugs when compared to the use of authorised medicinal products. But risk-assessed approaches to safety monitoring and dossier submission can be evaluated and attempted that seek to distinguish between the study of 'first in human' drugs and authorised drugs to be used within established indications. The distinction between commercial and non-commercial trials is not relevant, in itself, to the degree of safety reporting that must be made by the researcher to the sponsor. Nor is the distinction relevant to the level of safety reporting that must be made by the sponsor to the competent authority. *It is the limited quantity of safety data about a drug when measured against the potential risk to the subject that determines the level of safety reporting that must be applied in risk-based pharmacovigilance*. It is therefore difficult to understand why the distinction between commercial and non-commercial trials should be retained on the basis of the need to safeguard public safety. If my reasoning can be supported by further empirical evidence, then the Commission should consider whether the current division between commercial and non-commercial drug trials should be abolished.

Topic 2.2: More precise and risk-adapted rules for the content of the application dossier and for safety reporting

Consultation Item 11:

Answer: Yes

Consultation Item 12:

Answer: No comment. It is a matter for scientific/clinical evidence.

Risk-adapted regulatory requirements should be encouraged for the conduct of clinical research. As an example, in the United Kingdom, there is evidence that pharmacological or pharmacogenetic studies that are run on the back of recruitment to clinical trials, but which are otherwise independent of their outcome, and which require only an additional blood or tissue sample from the subject, are being required to submit to the same reporting and governance requirements that apply to fully fledged clinical trials. In such cases, the regulatory requirements should be adjusted and focused to the actual areas

of risk to the patient, namely the conduct of sampling procedures and the correct labeling and retention of samples. Rigid regulatory requirements can also stifle reflexive approaches to patient welfare in more subtle ways, by masking what is truly relevant. So, to remain within the current example, a pharmacogenetic study may yield results that are of clinical significance to individual patients. In such a case, the main ethical issue is not whether full safety monitoring should be applied to what is in effect a laboratory based study, but whether personal data protection methods are sufficiently adaptive to enable the subjects to remain anonymised but yet capable of being contacted should the need arise to administer counselling or therapeutic treatment.

I am frankly doubtful that anything will come of the current attempts to re-classify risk-based pharmacovigilance by reference to the marketing authorisation of the product or the phase of the trial. Discussions within the Road Map Initiative[26] indicate that any attempt to introduce a three-tier classification of studies based on the status of marketing authorisation for the drug will produce an unacceptably broad intermediate category. Trials of marketed drugs for new indications or within new populations will require additional risk-adapted measures that defy general classification. This is because few drugs have marketing authorisation in all member states. Therefore marketing authorisation cannot be treated as being synonymous with the usual standard of care in those member states. Uncertainty in the assessment of risk according to the marketing authorisation of the study drug also means that risk-adapted regulation cannot be applied merely on the basis of its phase. Furthermore, I have examined the outcome of several conferences devoted to the question of risk-based pharmacovigilance and do not yet see any common ground between industry and academic researchers that might result in a common set of safety reporting standards that make allowance for the exigencies of academic research. I recall one response from an industry representative very well; the US Food and Drugs Administration would not tolerate a relaxation in safety reporting standards so there was no incentive for the pharmaceutical industry to do likewise.

I advance the proposition that risk-based approaches to regulation, if they can be applied at all, should be applied only on a case by case [or protocol by protocol] basis. There should be sufficient flexibility in regulatory and governance rules to enable the competent authority and/or ethics committee to select requirements according to risks that are individually assessed on the facts of the protocol before them. This means more responsibility for those concerned in assessing protocols and therefore more skill will be

required of them. The Commission should explore this question very carefully. Instead of seeking simple fixes by allocating protocols to categories, what is really needed is a '*toolkit*' from which adapted regulatory responses can be selected according to individual circumstances. The research governance community should proceed by the examination of vignettes or model case studies from which risk assessed solutions can be developed and applied. It is an evaluation method that is based on casuistry.

So, in the case of a pharmacological study of the type shown in the example above, where the only additional interventions are for blood and tissue sampling, there should be no requirement for the study to comply with pharmacovigilance and safety reporting standards normally applicable to clinical trials. This is because adverse events will be limited only to those arising from the administration of the sampling procedures. Researcher accreditation, insurance and indemnification should be sufficient to cater for that risk. This is an alternative to redefining what the Directive means by a 'non-interventional trial'.

To provide adaptive research governance will require better synergy between national competent authority and ethics committee. I have already set out the case for a merger of these two bodies into a single composite regulator for clinical trials[27]. The Commission should consider whether risk-adapted regulatory solutions might be better administered by this new type of regulator within European Union member states. Does the reduction in the regulatory burden on the researcher necessitate a strengthening of the apparatus of the regulator?

Topic 2.3: Clarifying the definition of 'investigational medicinal product' and establishing rules for 'auxiliary medicinal products'

Consultation Item 13:

Answer: Yes

Topic 2.4: Insurance/Indemnification

Consultation Item 14:

Answer: Indemnification by Member States.

Insurance and indemnification is the most important question in the Concept Paper. I applaud the Commission for embracing the initiative for state administered insurance funds for injured trial subjects. I doubt that risk-based pharmacovigilance is readily achievable, but compensation funding is. I support the plan for indemnification from state compensation funds.

I note that the Commission proposes that indemnification by the state shall be optional. I do not understand what is meant by the use of the word 'optional' in this context. But if the Commission means that the divergence in national laws and insurance arrangements between member states is so great that no single prescriptive solution can be applied, then I agree. Member states must be left to implement their own arrangements but supported by means of inter-governmental cooperation and possibly by a separate Directive.

Conversely, I oppose the suggestion that clinical research studies of any type should be removed from the requirement to provide adequate compensation protection for their subjects. High value compensation claims can arise from minor clinical procedures incorrectly performed. It is fanciful to assume that research studies approximate to standard care are immune from costly compensation claims, even though the frequency of such claims may be low. Even proposed 'Type A' research studies must be insured against claims for injury. Again, I repeat the point that the research community must guard against becoming 'normalised' to hidden or misinterpreted risk. The TGN1412 study stands as a cautionary reminder of that.

I oppose the suggestion that competent authorities and/or ethics committees should engage in a process whereby they are expected to apply a sliding scale of insurance requirements based on the sponsor's assessment of risk or even upon their own prescriptive list of interventions requiring indemnity cover. It is impossible for an ethics committee to put a figure on a prospective compensation award, because there are too many unknown factors referent to the claimant. If there is an unforeseen claim of maximum severity that exceeds the level of cover, the claimant risks being left unprotected in the absence of any insurance pool established for that purpose.

Competent authorities and ethics committees can only consider risk-based approaches to clinical trial insurance with any degree of safety if there is some additional form of state protection for injured research subjects that is supplemental to that provided by the sponsor. That fund could be topped up by means of a levy on pharmaceutical companies.

I doubt that insurers could provide a reliable assessment of the risk of a clinical trial even if it were to be assessed according to the 'triage' classifications of research now being proposed in the course of these Consultations. It has been said that insurers in Germany adopt a risk assessment based on the number and type of interventions in a research study and that this approach has resulted in some arbitrary and inconsistent attributions of risk[28]. Is there any reason to assume that other insurers can do better?

Alternatives to state sponsored insurance arrangements have been considered in the course of the 2009/2010 Consultation. ICREL has recommended the development of 'block' packages for insurance in clinical research as an alternative to the insurance of individual studies[29]. There are potential difficulties with a block insurance approach[30]. I surmise at this time that block arrangements might lead to the marginalisation of rare disease research with high risk profiles. It might favour groupings of insured sponsors or studies according to risk profile rather than topical disease and which might prove fragmentary to research networks.

State sponsored insurance schemes that are accessible to academic researchers may do much to level the playing field between publicly funded researchers and their commercially sponsored counterparts in the drive to run more and better powered studies. If the current legislative division between commercial and non-commercial trials were also to be abolished, then these two factors combined might enable academic-commercial partnership research to be more readily facilitated. For example, it has been contended[31] that a two-tier research environment has arisen in Italy in the wake of state insurance legislation[32], because academic sponsors have difficulty in accessing affordable insurance for clinical trials conducted on a 'not-for-profit' basis. If the 'not-for profit' requirement were to be interpreted less strictly in favour of Italian state sector researchers acting in collaboration with industrial counterparts, and if added support were to be provided from an insurance fund maintained by the state, then the performance gap between the two sides of the research community might be lessened.

Topic 2.5: Single Sponsor

Consultation Item 15:

Answer: No. The question is wrongly framed.

The Directive never contained a prohibition against multiple sponsors. References to the sponsor in the singular should include the plural form. This is how UK law has approached the issue[33]. The European Commission has issued guidance in its *Questions and Answers on Clinical Trials* dated 28th July 2009 which specifically allow for an organisational grouping of researchers to become, in effect, multiple sponsors. Sponsors can also delegate their responsibility to agents, whilst still retaining legal responsibility for the duties of the sponsor. It is better to allow flexibility so that researchers can use multiple sponsorship arrangements if it is considered helpful to do so. This means leaving the current legal provisions as they are and issuing further clarification that the researcher has a choice in deciding sponsorship arrangements. Is multiple sponsorship truly burdensome or have researchers failed to develop adequate research infrastructures that would enable optimal collaboration between multiple sponsors?

Topic 2.6: Emergency Clinical Trials

Consultation Item 16:

Answer: Yes. But there are legal/ethical issues that must be resolved also.

This proposal is overdue. It is necessary to harmonise national laws prescribing the circumstances in which an incapacitated adult can be enrolled into emergency clinical trials and without the prior informed consent of a legal representative. Failure to deal with this problem in the original cast of the Directive has lead to legal divergence between member states and this has lead in turn to adverse consequences for research. The circumstances of the TROICA study are illustrative. It has been contended that the consequences of this study prompted the enactment in the United Kingdom of the current regulations providing for emergency research. The United Kingdom could not host the study on the state of the law as it formerly applied. The TROICA study could only go ahead in those member states with national laws that enabled this type of emergency research to be conducted. Those national laws[34] waive the requirement for informed consent if the treatment and associated research must commence as a matter

of urgency[35]. In so doing, they avoided the stipulation of Article 5(a) of the Directive that the consent of a legal representative is required for recruitment of an incapacitated adult into a clinical trial. The Good Clinical Practice Directive allowed these member states sufficient latitude in its associated guidance to enable them to maintain their national laws. These national laws are predicated on the implied premise that clinical trials are of therapeutic benefit to the subject who is enrolled in them. The purpose of this response is to show that this premise is false. A new legal and ethical basis for research involving incapacitated adults must therefore be incorporated into a revised Clinical Trials Directive.

The Commission should address the following issues;

1. *Those member states with national laws that waive the requirement for informed consent upon the ground that the research is therapeutic and/or necessary and in the best interests of the research subject do so upon the basis of a legal category error*. So the Directive needs to be recast to ground emergency research upon the foundation of a deferral of consent, as Directive Article 5(a) requires, and not upon the waiver of consent. This is because clinical research involving comparative drugs and treatments proceeds on the principle of equipoise. Equipoise presumes a genuine uncertainty as to the therapeutic benefits of the drug or treatment under investigation. Equipoise is inconsistent with the notion of an expectation of direct benefit or no additional risk to the recipient subject. Furthermore, if there can be no real expectation of direct benefit to a patient in a clinical trial conducted in equipoise, it follows that it cannot be described as therapeutic research. Therefore it is a fallacy to predicate the conduct of emergency clinical research upon the legal basis that the research is necessary for the benefit of the incapacitated patient.

2. The Commission must therefore devise a harmonised means of seeking approval for clinical trials involving incapacitated adults in those cases in which it is anticipated that there will be no time to consult a legal representative on the matter of consent or the best interests of the patient. This would necessitate a consideration of when informed consent should be obtained and who should be consulted for this purpose and is to be decided on a case by case basis. The national ethics committee is best placed to decide these questions at first instance and not the courts, because the ethics committee is better informed of the protocol. The United Kingdom enacted regulations that enable ethics committees to set out arrangements for researchers

whereby consent could be obtained after the emergency clinical trials had been commenced[36]. The other member states should consider this model as an example to follow.

3. The problem is not simply the absence of harmonised legal rules as to when the incapacitated adult can be enrolled into emergency research. There are additional problems in other member states concerning the procedural mechanism that needs to be undertaken in order to seek lawful approval for the enrolment of incapacitated adults into any form of [non-emergency] medical research. In Germany and Italy, for example, there must be an application to a court to determine which legal representatives are to be consulted on patient enrolment. This could delay the commencement of research. The power for research subjects to nominate and for researchers to designate the persons to be consulted on matters of consent and the subject's best interests, but without the need for a court to rule first upon the matter, is an important measure for reform. It has been suggested that the Directive should set out a list of persons who can be consulted [relatives, carers, etc.] and should abandon its single unqualified reference to legal representatives on the reasoning that its wide scope for interpretation is open to abuse[37].

4. There are basic inconsistencies between the Directive and key international guidelines as to when research involving incapacitated adults can be commenced. The Directive requires direct benefit to the individual subject, outweighing the risks to him, as a condition of the recruitment of an incapacitated adult into a clinical trial[38]. ICH GCP does not require a direct benefit to the research subject provided that, amongst other matters, the study is approved by an ethics committee, is not contrary to law, has low risk to the subject and minimises the negative impact upon him [39]. That is a basic inconsistency between the Directive and ICH GCP which must be resolved. Furthermore, the Helsinki Declaration and the Oviedo Convention do not distinguish between clinical drug trials and other forms of medical research. Those guidelines permit medical research without direct benefit to the subject provided that the research is intended to benefit the wider patient group and that the research entails minimal risk and minimal burden to the subject. In this way, these guidelines are in contradiction to the Directive[40].

5. Should a clinical trial of an investigational medicinal product be expected to produce a direct benefit to the patient that outweighs the risks or should it suffice that the research is capable of producing a future benefit to the patient group to which the patient belongs? Should there be different requirements for clinical drugs trials as opposed to other types of medical research on the requirement for direct benefit versus group benefit? *Provided that the risk to the incapacitated subject is minimal*, does it matter that he receives no direct benefit in a clinical trial provided that the wider patient group might do so? Does emergency research involving incapacitated adults place added importance on the need for direct benefit or does the same risk/benefit assessment apply as to non-emergency research? Should the Directive be amended to reflect the relevant guidelines or must the guidelines themselves be revised?

6. Does the current distinction between therapeutic and non-therapeutic clinical trials make any sense? We might define a therapeutic clinical trial as one that is expected to produce a quantifiable direct benefit to the patient. So can an incapacitated adult in the control arm of a randomised clinical trial to which equipoise applies ever be said to be in a therapeutic clinical trial? As mentioned above, the definitional problem is compounded by the fact that ICH Good Clinical Practice Guidelines[41] permit non-therapeutic trials [that by implication have no anticipated direct benefit to the patient], provided that, amongst other matters, they have low risk to the subject and minimise the negative impact upon him. As such there seems to be a palpable conflict between the Clinical Trials Directive[42] and the ICH Guidelines on the need for a clinical trial to yield a direct benefit to the incapacitated subject that outweighs the risks to him. In these circumstances, should the distinction between therapeutic and non-therapeutic clinical trials be expunged from the guidelines and from legislation as serving no useful purpose?

7. If it is accepted that the requirement for direct benefit to the trial subject is a misconception, then what matters is the degree of risk and burden to the trial subject. The Directive stipulates[43] in the alternative that the there must be 'no risk at all' to the trial subject. In the context of a clinical trial in equipoise, how can this total eradication of research risk ever be guaranteed? Some commentators[44] recommend that the proper test should instead be one of 'minimal risk'. The revised Declaration of Helsinki and CIOMS Guidelines also adopt reference to minimal risk. Thus;

> "In our view, the appropriate threshold is that the research components entail no more than 'minimal risk'. Unfortunately, this does not fit neatly with the current phrasing of the Directive ("no risk at all'), hence we used the words 'no serious risk at all' in the italicised clarification above. That said, we intend it to mean the same thing as minimal risk. If this suggestion were followed, vulnerable individuals unable to give consent would not face undue risks for the sake of society; by the same token, though, this community of people would not be left vulnerable to poor medical care, which could be improved upon by low risk medical research."

8. In order to balance risks and benefits to an incapacitated adult in a clinical trial, the same commentators recommend that a better test be adopted. This is the *component risk analysis* propounded by Weijer and Others. I direct the Commission specifically to these arguments[45]. These commentators explain the approach as follows;

> "…the therapeutic components of a randomised-controlled trial that should meet the standards of clinical equipoise. The research components are analysed separately. Clinical equipoise ensures 'a rough parity in terms of benefit, harm, and uncertainty between the procedures that patients would receive as a part of clinical practice and therapeutic procedures [he receives] in a clinical trial. This means the patients' therapeutic goals are no better and no worse off than if they did not participate in the research. The additional risks they face due to the research components of the trial are the result of their bodies being used to answer scientific questions and should be monitored more closely
>
> There should be grounds for expecting that administering the medicinal product to be tested will produce a *therapeutic* benefit to the patient *equivalent to standard treatment* and outweighing the risks *of therapy* and produce *no serious research* risks at all (Authors' italics)."

9. The commentators recommend that the clinical research community develop complex risk comparison techniques that will enable answers to the questions that they pose. I recommend that these matters be examined within the ambit of any further consultation on specific amendments to the Directive.

Consultation Topic 3: Ensuring Compliance with Good Clinical Practices in Clinical Trials performed in Third Countries

Consultation Item 17:

Answer: Yes.

The use of the European Public Assessment Report could be a potent tool to block marketing authorisation for drug studies conducted in third countries that infringe European legal and ethical standards. Development of this tool for this purpose should be encouraged.

Time restraints and limitations on document size prevent me from making a fuller response. To assist the Commission, I am submitting a copy of my earlier response in 2010 to the European Medicine Agency's Reflection Paper on clinical trials conducted in third countries[46]. You may publish that document also.

Consultation Topic 4: Figures and Data

Consultation Item 18:

Answer: No.

Save to indicate that I was very interested to read the data relating to incidences of legal claims for compensation for clinical accidents at paragraph 7.3 of the Annex. I must remark that the accuracy of such data depends upon the willingness of insurers, pharmaceutical companies, CROs and state health authorities to disclose their data relating to claims received. The Commission did state that the data was very limited. It would be useful if the Commission could indicate if pharmaceutical companies were willing in any significant number to disclose their claims data. Is there any risk that the Commission's assessment of the cost feasibility of introducing state compensation arrangements might in any way be compromised by incompleteness in the data?

Dated 29th April 2011

END

[1] http://ec.europa.eu/health/files/clinicaltrials/docs/responses_2001-20/roy_toole_christopher.pdf

[2] Concept Paper section 1.3.1

[3] http://www.cioms.ch/publications/layout_guide2002.pdf at page 25.

[4] http://ec.europa.eu/health/files/clinicaltrials/docs/responses_2001-20/roy_toole_christopher.pdf at paragraph 6

[5] https://www.myresearchproject.org.uk/

[6] http://www.cioms.ch/publications/layout_guide2002.pdf at page 25.

[7] Directive 2001/20/EC, Article 3(2)(a)

[8] Directive 2001/20/EC Article 6(4)

[9] Directive 2001/EC/EC Article 6(3)(b)

[10] Directive 2001/20/EC Article 2(k)

[11] Directive 2001/20/EC Article 7

[12] Concept Paper section 1.3.1

[13] CIOMS Guidelines at page 25, Guideline 2

[14] Directive 2001/20/EC Article 6(3)(b)

[15] Roy-Toole C. Illegality *in the research protocol: the duty of research ethics committees under the 2001 Clinical Trials Directive*. Res Ethics Rev 2008; 4(3): 111-116.; Marc Taylor C, Saunders J, Davies H. *Research ethics committees and legal opinion (letter)*. Res Ethics Rev 2008; 4(4): 165-166; Roy-Toole C. *Research ethics committees and the legality of the protocol: a rejoinder and a challenge to the Department of Health*. Res Ethics Rev 2009; 5(1): 34–37; Roy-Toole C. *The 'New Governance Arrangements for Research Ethics Committees': policy-shift and equivocation on matters of illegal research.* Research Ethics Review (2009) Vol 5, No 4, pp.160-161

[16] http://www.dh.gov.uk/en/MediaCentre/Pressreleases/DH_117844

[17] http://ec.europa.eu/health/files/eudralex/vol-6/a/vol6a_chap2_2005-11_en.pdf

[18] http://ec.europa.eu/health/files/eudralex/vol-2/a/vol2a_chap2_2007-02_en.pdf

[19] Directive 2001/83/EC, Articles 32, 33 and 34

[20] Directive 2001/20/EC Article 2(k)

[21] http://www.hma.eu/uploads/media/VHP_version_2_March_2010.pdf

[22] Concept Paper section 1.2

[23] *The TGN1412 clinical trial: a 'normal' accident*,a 2009 lecture by Professor Adam Hedgecoe (Cardiff University)

[24] http://www.nres.npsa.nhs.uk/applications/proportionate-review/

[25] http://www.acmedsci.ac.uk/download.php?file=/images/project/129468115924.pdf at section 8.3, 8.4

[26] http://www.ebmt.org/2relatedmeetings/Report-RoadmapInitiativeFinalWorkshop17-03-10v3.pdf

[27] http://ec.europa.eu/health/files/clinicaltrials/docs/responses_2001-20/roy_toole_christopher.pdf

[28] EORTC Workshop: *The Need for Harmonisation of Clinical Trials Insurance in Europe* held on 28th June 2010

[29] ICREL Final Report: *Impact on Clinical Research of European Legislation*, 2009

[30] http://ec.europa.eu/health/files/clinicaltrials/docs/responses_2001-20/roy_toole_christopher.pdf

[31] G. Apolone and G. Capelli *Issues on Insurance for Clinical Trials and REC Liability: Impact of recent Italian laws and Implications for the ethical review process,* EFGCP Conference Rome 2010

[32] Italian Ministerial Decree of July 14th 2009 Official Gazette no. 213 of 14.9.2009

[33] http://www.ct-toolkit.ac.uk/_db/_documents/sponsorship.pdf

[34] The member states being; Austria, Belgium, France, Germany, the Netherlands, Norway and Spain

[35] Kathleen Liddell, Julian Bion, Douglas Chamberlain, Christiane Druml, Erwin Kompanje, Francois Lemaire, David Menon, Bozidar Vrhovac, and Christian J. Wiedermann *Medical Research involving incapacitated adults: implications of the EU Clinical Trials Directive 2001/20/EC* Medical Law Review, 14, Autumn 2006, pp. 367–417

[36] Medicines for Human Use (Clinical Trials) Amendment (No.2) Regulations 2006

[37] Kathleen Liddell, Julian Bion, Douglas Chamberlain, Christiane Druml, Erwin Kompanje, Francois Lemaire, David Menon, Bozidar Vrhovac, and Christian J. Wiedermann *Medical Research involving incapacitated adults: implications of the EU Clinical Trials Directive 2001/20/EC* Medical Law Review, 14, Autumn 2006, pp. 367–417

[38] Directive 2001/20/EC Article Recital (4), Article 5(i)

[39] ICH Topic E6 (R1) [2002] Guideline for GCP paragraph 4.8.14

[40] Erwin Deutsch, The Revised Declaration of Helsinki (Edinburgh 2000)

[41] ICH Topic E6 (R1) [2002] Guideline for GCP paragraph 4.8.14

[42] Directive 2001/20/EC Article 5(i)

[43] Directive 2001/20/EC Article 5(i)

[44] Kathleen Liddell, Julian Bion, Douglas Chamberlain, Christiane Druml, Erwin Kompanje, Francois Lemaire, David Menon, Bozidar Vrhovac, and Christian J. Wiedermann *Medical Research involving incapacitated adults: implications of the EU Clinical Trials Directive 2001/20/EC* Medical Law Review, 14, Autumn 2006, pp. 367–417

[45] Kathleen Liddell, Julian Bion, Douglas Chamberlain, Christiane Druml, Erwin Kompanje, Francois Lemaire, David Menon, Bozidar Vrhovac, and Christian J. Wiedermann *Medical Research involving incapacitated adults: implications of the EU Clinical Trials Directive 2001/20/EC* Medical Law Review, 14, Autumn 2006, pp. 367–417; C. Weijer and P. Miller, '*When are Research Risks Reasonable in Relation to Anticipated Benefits*?' (2004) 10(6) Nature Medicine 570–573; A. McRae and C. Weijer, '*Lessons from Everyday Lives: A Moral Justification for Acute Care Research'* (2002) 30 Critical Care Medicine 1146–1148; C. Freedman et al., '*Demarcating Research and Treatment: A Systematic Approach for the Analysis of the Ethics of Clinical Research*' (1992) 40(4) Clinical Research 653–660; C. Weijer, *'Ethical Analysis of Risk'* (2000) 28 J.L.M.E. 344–361.

[46] *EMA/712397/2009*