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

**UK RESPONSE TO CONCEPT PAPER**

## Introduction

This letter provides the UK Government's response to the Commission's public consultation on the proposed revision of the Clinical Trials Directive (2001/20/EC).

The UK Government is pleased to see the preliminary appraisal put forward for consideration in the Concept Paper published on 9 February 2011, and believes that the forthcoming review of the Directive provides an important opportunity to ensure that the EU maintains its position as an attractive place for the conduct of clinical trials necessary to the development of new medicines.

On most of the issues raised in the Concept Paper the UK strongly supports the Commission's proposed approach and welcomes the collaborative work that has gone into the development of the ideas the paper contains. We would, however, and on behalf of both commercial and academic researchers in the UK, as well as patients who participate in clinical trials, urge the Commission to prioritise the proposed redraft of this important Directive so that both the Member States and the European Parliament may begin the necessary formal negotiations with a view to an early agreement and implementation.

Our comments on specific issues raised in the Concept Paper are as follows:

## Adopting a risk adapted approach to the approval of clinical trials

As a result of discussions between Member States and the Commission, we had understood that the review of the Clinical Trials Directive would introduce the possibility of taking a risk adapted approach to the approval of all types of trials involving medicines. Although the Concept Paper references a risk based approach in several places (1.3.4, 2.1.1, 2.1.2, 2.2) it is not clear that the aim is to apply a risk adapted approach to the approval of all trials within the scope of the Directive. The UK strongly supports the adoption of a risk adapted approach to the approval of all categories of clinical trial that falls within the scope of the Directive and believes that this concept should be clearly set out in the revised Directive. This would include, where appropriate, provision for pre-assessment of risk by the sponsor, to be reviewed by the NCA on application. The UK has implemented a project that operates a risk adapted approach to trial approval, monitoring and data collection within the framework of the current Directive and we hope that this will provide evidence of how such a regime could

be adopted in the revised legislation. These risk adapted approaches have been developed in collaboration with Good Clinical Practice (GCP) inspectors and representatives of the academic research community to ensure that researchers and regulators apply them consistently. Improved guidance on the application of GCP that takes account of a risk adapted approach to the conduct of clinical trials would be helpful in this respect. The concept of risk adaptation is also to be extended to ethics review, looking at how application dossiers, Ethics Committee procedures/timelines and guidance could reflect the significance of the risks and ethical issues posed by different types of trial.

**1. Cooperation in Assessing and Following up Applications for Clinical Trials.**

We strongly support the need for an improved regime for the approval of multi-state clinical trials, and that this should be set out in the revised legislation. Our preferred approach would be broadly along the lines of the "coordinated assessment procedure" (CAP) set out in the Concept Paper but with some small differences:

(i) We believe that in order to ensure a robust single decision under the CAP all Member States (not just those concerned in the "1st wave" of applications) should be able to access, review and comment on the application via the central EU portal if they so wish. This would be fairer on Member States in a 2nd or subsequent wave of applications which would not, otherwise, have had any opportunity to input to the original decision. This arrangement would not, however, alter the principle that once a single assessment had been determined under the 1st wave of applications, that assessment would stand for all subsequent applications, and Member States would be obliged to accept that assessment or to "opt out" of the trial (as proposed in **1.3.2**). We are, however, conscious that such a system does need to provide properly for a review of the trial protocol by Member States involved in any 2nd or subsequent wave of applications who may not have chosen to review the application in the 1st wave. It should be possible to provide a mechanism under which a Member State could negotiate with the RMS from the first wave to request further information or protocol changes to meet their concerns, but that if he fails to do so, that Member State simply "opts out". We also need to establish a mechanism for all Member States to charge the trial sponsor a fee to cover costs associated with reviewing the protocol and collecting and analysing data arising from the trial in their territory.

(ii) The paper implies that the single EU portal will allow submission of documents for clinical trial and ethics committee approvals. Whilst we endorse this idea in principle, we believe this may be challenging to achieve in practice. As the Concept Paper acknowledges, ethics and local approvals are matters for each

Member State to undertake, and there may be significant differences in the information required (including information needed under legislation other than CTD 2001/20) and the formats used nationally to obtain that information. There will also be significant language challenges to address. Nevertheless, we believe that a single dossier (including the application to NCAs and a core set of data for ethics approval) to be submitted via the EU portal would be acceptable. Given the differing ways in which ethics approval will continue to be handled in Member States we will also want to retain the current arrangements that allow for a single "clock stop" within the process for a round of questions and answers between the trial sponsor and those approving the ethical dimension of a trial. It is essential that the portal can be linked to IT systems in Member States so that the core dossier can be linked to additional information required by review bodies at national level. The UK has developed an Integrated Research Application System (IRAS) that provides a single submission point for all research to be conducted in the UK which works well. We will want to be assured that any EU-wide system provides at least as efficient, robust and appropriate a system as that which we have developed for trials conducted in the UK.

(iii) Although parallel submissions are generally encouraged, we feel that the ability to make submissions to the Ethics Committee and NCA independently should remain an option available to sponsors. Ethics opinions are often used to 1) help develop the proposal and 2) to release funding for further development. This may be submitted months or even years before a submission to the NCA for CTA approval.

(iv) We therefore broadly endorse the position the Paper takes that only issues identified under **1.3.1(a)** should be subject to review by the CAP. However, the other issues in sections (a) to (c) are not a comprehensive description of what either the competent authorities or the ethics committees are required to review. The UK agrees with the concept that it is decided at Member State level who assesses what from Sections (a) to (c). However we would wish to restrict the assessment activity under the CAP to aspects in 1.3.1(a) that are assessed by all (or the majority) of NCAs; broadly similar to the current VHP. Including aspects which may be assessed by Ethics Committees in a number of Member States within the CAP will create significant processing complications and complexities within the MS, including inconsistency with established arrangements for approval of other clinical research, without any clear benefits. In particular, the UK believes that the design and relevance of the trial should be assessed as part of the ethical review under (b) rather than under the CAP, except insofar as they impact on matters within scope of NCAs such as subject safety. The UK also notes that

NCAs do not normally review all inconveniencies for trial subjects, only potential risks from administration of IMPs, and that these should be included in a broader risk-benefit assessment by the ethics committee at a national level.

(v) The UK believes that under **1.3.3**, the use of the CAP should not be mandatory for multi-state trials.

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(vi) We support proposals under **1.3.4** to introduce a more flexible approach to the approval of clinical trials (see comments above). The assessment of risk associated with a trial must take account of the risk to the trial subjects, and also the use to which the data collected in the trial are to be put (although we acknowledge that such trials will, in any case, be subject to GCP standards). Under such a regime we believe that following a pre-assessment by the sponsor, a notification system under which trials considered to be at the lower end of risk (Type A) could be allowed to start if after 14 days no objection has been raised by the competent authorities (and provided the trial has a favourable opinion from the Ethics Committee). We agree however that this form of tacit approval would not be appropriate under the CAP.

## 2. Better Adaptation to Practical Requirements and a more Harmonised, Risk Adapted Approach to the Procedural Aspects of Clinical Trials

The UK strongly supports the aims of the proposals to increase harmonisation of procedures across the Union and to adopt a risk adapted approach to the approval **and conduct** of clinical trials. Our comments on the proposals put forward in the concept paper are as follows:

(i) The UK agrees that the scope of the Directive should include all safety and/or efficacy trials of medicines, other than non-interventional trials. A significant problem with the definition of clinical trials is a consistent understanding of what constitutes efficacy and we would like to see improved clarity through a change to the definition or to associated guidance on this point. The UK supports the view that the solution to the problem associated with the definition of a non-interventional trial is to provide greater clarity either in the definition or in associated guidance on what does, and what does not, fall within scope of the Directive. The most problematic part of the definition of a non-interventional trial is interpreting what are additional diagnostic and monitoring procedures. In addition, the application of a risk adapted approach to the approval of all interventional trials would ensure that the level of regulatory oversight would be proportionate to the

risk. This should include as a minimum a reduced application content requirement and shortened approval times. For single state trials a notification only process for Type A trials with tacit approval, as implemented in the UK, could be introduced.

(ii) We fully support the analysis in **2.1.2** that academic/non-commercial trials should not be excluded from the scope of the Directive, most especially because trial subjects participating in such research are entitled to the same level of safety as those participating in commercial research. It is worth noting here that not all academic trials fall into the "low risk" category and some data from non-commercial trials may be used to support a marketing authorisation application. Neither is it always easy to determine a distinction in practice between trials conducted for or by an academic versus a commercial sponsor. Inclusion of such trials and application of a proportionate and risk adapted approach to their approval is the solution we would prefer to see the Directive adopt.

(iii) The UK also supports the proposal **(2.2)** that it would make practical sense to remove from the main text of the Directive and annex certain elements that are likely to be subject to adaptation, such as the content of trial application dossiers. Under revised Union rules these would need to be amended/updated by means of delegated acts. The UK would want assurance, however, that Member State experts would always be consulted and their views taken into account when delegated act provisions in this area were proposed by the Commission. The UK fully supports the provision for risk adapted rules, and other key aspects to be included in these delegated acts. Specifically with respect to safety reporting our overriding concern here, whichever mechanism is adopted, is to ensure that the revised legislation removes the current requirement for sponsors to provide SUSARs and annual line listings to Ethics Committees and limits safety reporting to ECs to no more than the Executive Summary of the DSUR.

(iv) We also fully endorse the problem statement concerning the use of so-called "auxiliary medicinal products" **(2.3)** that may be used in a variety of ways as an adjunct to an investigational medicinal product (IMP) that is the subject of a clinical trial. However, whilst the proposed change to the definition of an investigational medicinal product will help clarify the situation with regard to background therapy, it appears to complicate the issue with regard to Phase IV trials (trials with marketed products). Since marketed products are intended for placing on the market and not intended for use in research and development trials, they are subject to the provisions of Directive 2001/83/EC. The proposed revision to the definition of an IMP describes them as subject to Article 3(3) of 2001/83/EC (that is, products intended for use in research and development trials, and not therefore

subject to the provisions of Directive 2001/83/EC itself). This change seems to remove the possibility of marketed products meeting the definition of IMPs, and, thus, removing Phase IV trials from the scope of the Clinical Trials Directive (2001/20).

(v) In respect of the issue of insurance and indemnity provided by the sponsor or investigator of a clinical trial **(2.4)**, we cannot support either option put forward in the Concept Paper. The UK believes that the parties involved in the design, management and conduct of a trial should always have an appropriate level of insurance/indemnity to meet the costs of harm to participants for which they are liable, regardless of the type of trial in which they have participated, and that this should be made clear in the Directive. At present some large pharmaceutical companies believe that it is sufficient, and in compliance with the Directive, to "self insure" against claims for damages from trial participants. The UK believes that this is unacceptable – there have been instances in which very large companies have failed and if this were to occur, participants in any clinical trials sponsored by them would, in effect, have no insurance against harm at all. We would therefore welcome clarification in the revised Directive that insurance or indemnity must be provided by a legal entity separate from the insured. However, it is not, in our view, the role of EU legislation to address ways in which this might be achieved (as would be the case if the Directive were to include an obligation on Member States to indemnify for damages incurred during clinical trials), especially as these are likely to need to vary widely from one Member State to another.

(vi) We agree with the assessment in the Concept Paper of the current problems associated with a "single sponsor" **(2.5)**. We propose that the revised Directive should more clearly make the distinction between "responsibility" for the conduct of a trial and "liability" in the case of damage to a trial participant. Responsibilities for study oversight would need clearly to be defined. We agree that improved harmonisation of procedures will go some way to resolving current difficulties. We remain committed, however, to flexible provisions for sponsorship that encourage effective collaborations, such as bodies taking joint responsibility, or allocating responsibility amongst themselves, for carrying out the functions of sponsor.

(vii) The UK supports the proposed approach to resolving current difficulties in respect of emergency clinical trials **(2.6)** and has developed a national regime very much along the lines proposed. In introducing this concept into the Directive it will be important that the provisions are carefully considered but that they retain sufficient flexibility to ensure that they can take account of national cultural differences and healthcare delivery regimes.

## 3. Ensuring Compliance with Good Clinical Practices in Clinical Trials Performed in Third Countries

(i) The UK accepts the view that application of Good Clinical Practice (GCP) standards in the conduct of clinical trials in 3rd countries is to be encouraged. We also accept that the Union must insist that GCP standards must be applied in respect of clinical trials conducted in 3rd countries where the data are used to support an application for a marketing authorisation for a medicine in the EU. However, we would hesitate to endorse a policy that would place an obligation on the Union to press for GCP standards to be applied to every trial conducted outside the EU where, in many cases, the results of such trials will only ever be used for local purposes and never to support an application for an EU marketing authorisation for a medicine.

## 4. Additional quantifiable information

We propose that in redrafting the EU legislation the Commission should consider whether to drop an explicit reference to the Declaration of Helsinki. Reference in the current legislation to the 1996 Declaration is confusing and has been superseded. Whilst it is essential that the rules for approval and conduct of clinical trials respect the principles that underpin the Declaration, and the legislation should make that clear, we propose that reference to any particular version of the document should not be necessary and could cause continued confusion.

We look forward to seeing the published responses to this consultation, and to the early adoption by the Commission of the revised legal texts.