UK RESPONSE TO THE COMMISSION'S CONSULTATION ON REVIEW OF THE CLINICAL TRIALS DIRECTIVE

General points (consultation items 1-3)

1. The introduction of legislation aimed at harmonising the way in which clinical trials conducted in the EU are authorised and at improving the reliability of data generated in those trials has not been without challenge, as the Commission has acknowledged. The Clinical Trials Directive has:

- conferred benefit in providing an EU regulatory basis for Phase I clinical trials;
- established standards of Good Clinical Practice (GCP) in the conduct of clinical trials;
- ensured that both Ethics Committees and National Competent Authorities work to common timelines; and
- significantly improved collaboration and understanding between authorities with greater networking and information sharing..

2. However, the Clinical Trials Directive has fallen short in its aim of harmonising the process of authorisation of clinical trials to be conducted in multiple Member States of the EU.

3. It has also led to development of large numbers of guidelines, and the establishment of two EU groups (the Commission's "ad-hoc" group and the Clinical Trials Facilitation Group established by the Heads of Medicines Agencies) with the overall aim of improving application of the Directive's provisions. Some of the guidance now available would have been of great value at an earlier stage of the regime, when Member States were contemplating the transposition of the EU legislation. Their late introduction has, in our view, contributed to the lack of consistency between Member States in implementation of the Directive provisions and in the persistent lack of harmonisation across Member States. Further problems have arisen because of the lack of clear definitions in the current legislation for some terms and procedures. The UK therefore agrees with the Commission's assessment that there is a need to address the shortcomings of the current legislation and to make recommendations for improvement.

4. Academic researchers in the UK have consistently reported that the Clinical Trials Directive has made the research environment significantly more difficult and bureaucratic. The MHRA and the Medical Research Council (MRC) are leading a project to identify and address specific areas of concern. In particular, the project is looking at developing a risk-adapted approach to the regulation of trials, improving communication with the academic research community and improving training and development opportunities for

academic researchers. This work will continue into 2010 and will continue to inform the UK position on the Commission's proposed review of the clinical trials legislation.

5. However, we have also seen a number of benefits arising from implementation of the Clinical Trials Directive in the UK. In particular, a single ethical opinion within 60 days has been consistently achieved, simplifying application procedures and reducing timelines. The requirement of the Directive for collaboration between Ethics Committees and the NCA has also been addressed through a Memorandum of Understanding, providing a clear statement of the roles of the competent authority (MHRA) and research Ethics Committees, closer joint working and explicit procedures for exchange of information. This has led to greater understanding of the respective responsibilities of these organisations, minimised duplication and lessened administrative burdens on those conducting clinical trials in the UK. Our organisations increasingly operate within a defined national framework supported by integrated information systems. This coordination is also valuable in protecting participants in health research outside the scope of the Directive. We recognise the benefits that could come from greater consistency across the EU, but believe that this should not be at the expense of closer coordination already achieved between regulators and institutions in each Member State.

In summary, the UK:

- ***Believes that the Clinical Trials Directive has brought some benefits in regulating trials conducted in the EU – especially EU regulation of Phase 1 studies;***
- ***Welcomes the introduction of Good Clinical Practice standards – especially in the conduct of non-commercial trials;***
- ***Recognises that the Directive has resulted in better collaboration and understanding between authorities;***
- ***Considers that it has fallen short in its aims to harmonise procedures across the EU;***
- ***Supports the Commission's initiative to review the operation of the Clinical Trials Directive.***

Key issue 1: Multiple and divergent assessments of clinical trials

Assessment by NCAs **(consultation item 4)**

6. The consultation document sets out several options for streamlining NCA assessments and reducing scope for differing outcomes. These include:

- Reliance on voluntary cooperation between Member States under the Voluntary Harmonisation Procedure (VHP);

- Streamlining through establishing a procedure similar to the "decentralised procedure" available for authorisation of medicinal products;
- Introducing on a voluntary basis a single assessment for the whole of the EU to be undertaken by a single body drawing on the scientific expertise at EMEA and using decision-making powers of the Commission.

7. The UK has carefully considered the implications of the various options proposed. We have concluded that the UK could not support a centralised process for assessment of any clinical trials – including multi-state trials. There are several reasons for this:

- A centralised clinical trials assessment (CTA) risks losing the clear benefits of closer collaboration between the Competent Authority and Ethics Committee in each Member State. In the UK we have set out the responsibilities of each of the organisations in a Memorandum of Understanding, which has increased awareness of the role of the MHRA and the ability to seek information and assurances where necessary. Specifically the MHRA has overall responsibility for oversight of safety of clinical trials and this has increased the confidence of Ethics Committees in the regulatory system as a whole and allowed them to focus on their own role. All this would be more difficult to achieve with a more remote EMEA-administered CTA process;
- A central assessment and authorisation that relied on EMEA expertise for some CTAs raises questions about competence, particularly as the resulting decision would have a public health impact in the Member States concerned. Member States would retain national competence for single Member States trials;
- A central assessment that relied on Member State review would lead to establishment of another expert committee comprising Member States and an arbitration process would be needed. This would inevitably lead to extended approval times for clinical trials in Europe, especially as resources devoted to clinical trials assessment varies widely across Member States;
- Only around 25% of clinical trials involve more than one Member State, and the practice of multi-state trials is rarer in academic trials than in commercial trials. This highlights the importance of a robust national system that will continue to apply to the 75% of all clinical trials that are conducted in a single Member State.

8. For these reasons the UK would prefer to see improvement in and formalisation of the current VHP process for the authorisation of multi-national trials that would mirror the decentralised/mutual recognition procedures that operate for licence applications. This might most usefully be achieved by establishing the procedure in law, similar to the formal structure underpinning the CMD(h). This formalised procedure would require a secretariat, and an arbitration and conciliation group to facilitate agreements between

Member States. The VHP could draw on the expertise available nationally from Member States - but need not oblige all Member States to participate. However, we recommend that participation in decision making on a particular trial is not limited only to those Member States concerned, so that the approval process will not be re-opened if the sponsor later decides to conduct the trials in additional Member States.

In summary, the UK:

- ***Does not support a centralised procedure for authorisation of any multi-state trials;***
- ***Supports the formalisation of the VHP in law as a process for multinational trials;***
- ***Supports robust national procedures as these will continue to be required for the substantial numbers of single state trials.***

Assessment by Ethics Committees **(consultation item 5)**

9. The application of ethical principles remains a clear national responsibility and is subject to cultural differences between Member States. The UK agrees with the Commission's view that a single ethical approval for clinical trials undertaken in several Member States would therefore be unacceptable, and unworkable. We have considered the three options put forward in the consultation paper:

One-stop shop for submission of assessment dossier

10. Application systems must reflect the different requirements for national competent authorities and ethics review. A standardised application dossier for NCAs and Ethics Committees would conflict with the objective of clarifying the roles and responsibilities of each body and increase the risk of duplication of review. The UK also considers that a standardised dossier for submission to Ethics Committees in each Member State would be impracticable because:

- It would be very difficult to reach agreement on a standardised form reflecting the specific requirements of ethics committees and the interfaces with other review processes in each Member State, for example host institution approval. If committees had to request further information during ethical review to address perceived gaps in the dossier this would lengthen the process and defeat the objective;
- Language issues would need to be addressed. Ethics Committee members are usually volunteers, including lay people. Not all will be willing or able to assess an application dossier written in English. There is a risk that membership would become less representative of their communities;

- Implementing and maintaining a Community-wide application system with electronic interfaces with national information systems would be complex and expensive;
- Standardisation of documents such as the subject information sheet, consent form and letters of invitation from clinicians would be difficult to achieve given cultural differences and variations in trial setting in each Member State;

In conclusion, attempting to standardise applications to Ethics Committees may lead to an increase in negative opinions.

11. We would also draw attention to the Integrated Research Application System (IRAS) developing in the UK which will provide for a single submission of data for any proposal to conduct research within the UK, supplying data needed by the NCA, Ethics Committees and other approval bodies. This regime provides for a "one stop shop" within the UK which we believe will deliver significant benefits for sponsors of all research to be conducted in the UK, but which, for reasons explained above, would not be appropriate for implementation across Member States.

Strengthening networks of national Ethics Committees involved in multinational clinical trials

12. The UK sees some merit in establishing a network of Ethics Committees to discuss major issues in ethics review such as recruitment to trials in emergency treatment, and to provide shared training. We propose that such a network should engage with overarching national Ethics Committees (such as the National Research Ethics Service (NRES) in the UK), rather than individual and local committees. At this stage the priority should be on improving networks within Member States - networking should not extend to attempts to harmonise the ethical review of particular trial applications.

Clarifying the respective scope of assessment of NCA and Ethics Committees.

13. The UK strongly supports this option and has already taken steps to do this in the UK with benefits both in harmonising the assessment process and at the same time strengthening the protection for subjects. A Memorandum of Understanding has been signed between the MHRA and the UK's National Research Ethics Service and the Gene Therapy Advisory Committee (the national committee responsible for reviewing trials of gene therapy medicinal products in the UK). This sets out the respective roles and responsibilities of each body and enables Ethics Committees to raise questions and resolve concerns quickly through direct communication. The benefits include:

- Avoiding unnecessary duplication and conflicting views in the initial assessment of a trial, simplifying the process for trialists;

- Providing assurance to Ethics Committees in areas where they lack the necessary expertise or resources, allowing them to focus on ethical aspects of trial applications;
- Enabling additional information to be brought to the attention of the MHRA where appropriate, strengthening the regulation of trials and the protection of trial subjects;
- Clarifying that the decision to suspend or terminate a trial rests solely with the MHRA.

The UK believes consideration should be given to including a clear statement of the respective roles and responsibilities of NCAs and Ethics Committees in the Directive.

In summary, the UK:

- ***Does not support a "one-stop shop" for submission of the assessment dossier to NCAs and Ethics Committees;***
- ***Supports the establishment of an EU wide network of Ethics Committees and the organisations that are responsible for their management;***
- ***Opposes any move to harmonise ethical review across the EU;***
- ***Recognises the benefits that could come from greater consistency across the EU;***
- ***Recognises the benefits of closer coordination between regulators, Ethics Committees and other institutions within each Member State which is also valuable in protecting participants in health research outside the scope of the Directive;***
- ***Proposes that the Directive should set out the respective responsibilities of regulators and Ethics Committees;***
- ***Opposes cross-EU harmonisation measures where these could disrupt well coordinated and effective frameworks of implementation in each Member State.***

Key issue 2: Inconsistent implementation of the Directive (consultation items 6-8)

Substantial amendments

14. The UK agrees with the Commission's assessment that the Clinical Trials Directive has resulted in differing interpretation by sponsors of "substantial amendment" to trial protocols.

- ***The UK believes that this should be resolved by better and clearer definitions within the legislation/guidance.***

Reporting of SUSARs

15. The UK agrees with the Commission's view of the SUSAR reporting scheme. Throughout Europe there is a disparity in reporting levels and categorisation of SUSARs. This is partly because Member States have different technical capabilities for e-reporting and partly because functionality of the Eudravigilance database is inadequate. Some Member States have also expressed concerns about confidentiality of data and the purposes for which it may be used.

16. The current disparity in reporting levels and categorisation across Member States must be resolved if we are to be able to provide assurances about the safety of patients participating in clinical trials in the EU. We must also find a way to resolve the problem of SUSARs already reported to Eudravigilance that we are currently unable to review. The UK also believes that the need for Member States to maintain their own facility for oversight of clinical trials will continue for the foreseeable future until Eudravigilance functionality is confirmed

17. A feature of the arrangements in the UK is that Ethics Committees are not expected to review Annual Safety Reports (ASRs), SUSAR reports or line listings, as they are able to rely on the MHRA to exercise effective oversight of the safety of the trial in consultation with other NCAs as appropriate.

18. The UK would welcome a change in the Directive to remove the requirement on the sponsor to provide safety reports (ASRs/SUSARs) to Ethics Committees which is burdensome, confuses the respective roles of the two bodies and is unnecessary providing that clear procedures are in place for notifying the Ethics Committees of any change to the safety profile. We believe that removing this requirement would reinforce the understanding that the competent authorities are primarily responsible for safety issues arising from clinical trials. It will continue to be important, however, to ensure that Ethics Committees are informed by the competent authorities about issues affecting the safety of patients involved in the trials they have approved. Removing the requirement for reporting direct to Ethics Committees would also reduce the administrative burden on sponsors.

In summary, the UK:

- ***Supports clarification of the rules on SUSAR reporting – including improved guidance on timeframes for SUSAR reporting - to resolve current disparity in reporting levels and categorisation across Member States;***
- ***Supports the continued development of the Eudravigilance database;***
- ***Proposes an appropriate transition period and demonstrations of Eudravigilance's full functionality before accepting a single reporting system;***

- ***agrees (as set out in section 4.2 of the consultation document) that the incoherent regime of transmitting and processing information on SUSARs leads to an increased risk of undetected factors influencing the risk-benefit balance;***
- ***Will continue for the foreseeable future to run a national reporting system alongside Eudravigilance;***
- ***Supports removal of the requirement for sponsors to provide SUSARs and annual safety reports to Ethics Committees.***

Scope of the Directive (interventional/non-interventional clinical trials)

19. The UK agrees with the Commission's analysis that there are currently circumstances in which the distinction between interventional and non-interventional trials is not clear, particularly in cases where additional diagnostic testing or monitoring procedures are involved. Non-interventional trials are currently out-with the scope of the Directive, but there are differences in interpretation across the Member States with some non-interventional trials – in particular where they require patients to undergo more testing than they would otherwise be subject to (eg blood tests or similar) - being considered "interventional". The UK considers that improved EU guidance is required to ensure that sponsors and NCAs have a clear understanding of the type and level of additional interventions that will qualify a trial as "interventional".

- ***The UK supports the Commission's view that interventional/non-interventional definitions should be clarified in EU guidance with a view to harmonising application of the definitions across the EU.***

Review the Clinical Trials Directive or replace it with a Regulation?

20. Whilst the option of replacing the Directive with a Regulation as the legislative instrument governing the clinical regime for the EU may appear superficially attractive as a means of reducing the scope for variation in implementation at national level, the UK believes that this could equally well be achieved by other means. In particular, the current Directive needs to be fully implemented and the concerns and uncertainties about current definitions as set out in the consultation document need to be addressed. The UK believes that a Regulation, despite providing a common legislative basis for clinical trial regulation across the EU, will not fully overcome the differences in interpretation that currently occur between Member States both by sponsors and NCAs.

21. Whilst we acknowledge that a Regulation would also provide a vehicle for introduction of a centralised procedure for certain categories of clinical trial, the UK cannot see any value in such a regime and particularly as such a high percentage of trials (75%) are conducted in a single Member State.

In summary the UK:

- ***Does not support any form of centralised procedure for the approval of clinical trials;***
- ***Would prefer to see the current Directive amended to address the concerns expressed in the consultation document.***

Key issue 3: Regulatory Framework not always adapted to the practical requirements (consultation items 9-13)

Requirements not always risk commensurate

22. We agree with the Commission's assessment of the shortcomings of the current rules which take a "one size fits all" approach and do not permit an appropriate response to the approval of trials according to their potential risk. We also believe that the designation of trials as "commercial" or "non-commercial" is unhelpful in determining how they should be regulated. As outlined in paragraph 19, certain low risk trials may become interventional simply because of the inclusion of additional blood tests on what is otherwise normal standard care and this can create difficulties for investigators. The UK believes that the approach to regulation should be fully risk based, and that the legislation and underpinning guidelines need better to reflect a risk-based approach to the regulation of all aspects of clinical trials. Whilst there are already many ways that sponsors could adopt a risk based approach based on current guidelines the references are dispersed throughout Volume 10 and in relation to some areas, such as monitoring, too sparse. For those researchers operating at the low risk end of the spectrum the relevant guidance is effectively unobtainable.

In summary, the UK:

- ***Supports the development of a risk-based approach to the regulation of all clinical trials, and that in this respect a determination of trials as "commercial" or "non-commercial" is unhelpful.***
- ***Supports the development of specific guidance on how risk adapted approaches can be implemented, covering all trials but aimed particularly at those operating at the low risk end.***
- ***Supports the need for improved guidance to clarify those low risk trials that are interventional/non-interventional.***

Single sponsors

23. The UK agrees with the Commission's analysis of the single sponsor issue. We believe that the concept of a single sponsor for multinational trials has had a negative impact on the functioning of these trials, particularly amongst academics, who will not or

cannot accept legal responsibility or provide insurance cover for sites in other Member States. Problems arise as the lead sponsor cannot be sited in all Member States conducting the trial, and so can have no real oversight of such trials. This also has implications for Member State competent authorities in holding sponsors to account for matters arising in clinical trials where the sponsor is not available in their territory and this in turn could have significant public health implications.

24. The UK believes that the solution to this problem is to allow shared sponsorship both within and across Member States in which the trial is conducted. There would need to be a clearly documented arrangement drawn up between parties involved in clinical trials, and any new proposal would need to be flexible enough to allow both delegation and sharing of responsibilities.

In summary, the UK:

- ***Supports changes to the legislation to allow sponsors in each Member State of a multinational trial to alleviate the single sponsor issue which has had a negative impact – particularly on academic multi-state research.***

Review of the existing Directive and excluding clinical trials of "academic" sponsors from the scope of the Directive

25. The UK agrees with the Commission that that since implementation of the Directive there have been some problems with conducting academic clinical trials. Many of these problems have arisen because the way that these trials are funded and organised can often be intrinsically different from commercial trials. This should not, however, lead to a conclusion that such trials should be excluded from the scope of the legislation. Academic trials cover a broad spectrum, from studies that are extremely low risk, to those that are at the cutting edge and involve "first in man" studies. The UK strongly believes that patients involved in academic trials have a right to expect the same level of protection as those participating in commercial, industry-sponsored trials. As the Commission has also pointed out, should such studies be excluded from the scope of the legislation, it would not be possible to use their results within an application for a marketing authorisation in the EU. The regulatory approach should be firmly focused on the type of trial, rather than on the status of the organisation/sponsor that will be conducting it.

In summary, the UK:

- ***Would strongly oppose complete exclusion of academic or non-commercial trials from the scope of the Directive;***
- ***Would advocate a risk-based approach to regulation of all trials that focuses on the risk associated with the trial rather than on the sponsor.***

Key issue 4: adaptation to peculiarities in trial participants and trial design (consultation items 14 & 15)

Paediatric trials

26. The UK fully supports the aims and objectives of the Paediatric Regulation in promoting the development of medicines authorised for the treatment of children. We strongly believe that all relevant provisions in EU legislation should support and not provide obstacles to these aims. In particular, restrictions on the provision of treatment in emergency situations that have inhibited the use of appropriate experimental treatments in the paediatric population is of particular concern. Additionally peculiarities in the way sick children may be managed through specialist centres and later local hospitals can lead to significant bureaucratic difficulties in setting up trials which may reduce the number of trials conducted.

Informed consent in emergency situations

27. The UK agrees that in this review the Commission must look at consent in emergency situations. A number of Member States - including the UK - have devised a process to allow for recruitment in emergency situations prior to consent, and we suggest that the Commission reviews these in considering the best way to resolve this issue. The UK legal provisions allow for obtaining retrospective consent from the subject or legal representative, enabling continuing participation in treatment and use of the data generated. The provisions apply to both adults unable to consent for themselves and to minors.

28. There are also issues about the use of personal data from those patients who have been entered into trials in emergencies. We would want to avoid publication of personal data in situations where the patient has entered into the trial without informed consent. The revised legislation should ensure that personal data from patients entered into trials under emergency situations is protected.

In summary, the UK:

- ***Believes that the clinical trials regime should support the aims and objectives of the Paediatric Regulation;***
- ***Strongly supports a revision of the system to ensure that consent in emergency situations can be obtained, including for children where appropriate;***
- ***The revised regime must provide for retrospective consent and use of data generated.***

Key issue 5: ensuring compliance with GCP in clinical trials conducted in 3rd countries (consultation item 16 & 17)

29. Increasingly trials that provide data included in applications for marketing authorisations within the EU are conducted in 3rd countries. In these circumstances the UK considers that it is essential that all efforts are made to ensure such trials are conducted in accordance with standards of Good Clinical Practice (GCP) that apply within the EU. However, it is entirely possible that many clinical trials conducted in 3rd countries are conducted for wholly internal and domestic purposes. It would seem inappropriate for the EU to adopt a policy that would imply some jurisdiction over trials conducted in such circumstances.

In summary, the UK:

- ***Agrees that trials conducted in third countries should be subject to GCP wherever the data generated will be used to support an application for a marketing authorisation within the EU.***