Response to the European Commission consultation on the revision of the Clinical Trials Directive 2001/20/EC

The National Health Service (NHS) is one of the largest publicly funded healthcare systems in the world, providing the majority of healthcare in England. The NHS is committed to the principle of universal access to healthcare which is free at the point of use. Every 36 hours the NHS sees over one million patients who make use of a wide range of health services ranging from primary care, in-patient care, long-term healthcare, ophthalmology and dentistry. The NHS is also the largest employer in Europe with more than 1.5 million people on its payroll.

The NHS has a strong history in clinical trials and, through its structure and access to patients and patient databases, can play a vital role in the development and uptake of innovative new medicines and technologies. Furthermore, clinical trials in the UK have made a large contribution to improved healthcare delivery around the globe and there continues to be enormous research potential in the NHS with academic and commercial partners.

In recent years however, the UK has lost ground internationally as a leading clinical trials environment. A 2009 UK government report[1] showed that the UK's involvement in global clinical trials dropped dramatically from 6% in 2002 to 2% in 2006, while the percentage of EU products in clinical trial development in the UK fell from 46% in 2002, to 24% in 2007. In addition, end of year figures for 2009 from the UK Department of Health indicate that the number of mid-stage, late-stage and post-approval clinical trials fell from 728 in 2008 to 470 in 2009, its lowest level in the past decade. Early stage trials fell to 210, the lowest in five years. There is an urgent need to improve the climate for clinical trials in the UK. It is our view that a review of the existing EU Clinical Trials Directive can help us to achieve this.

This response has been coordinated by the NHS European Office[2] in consultation with NHS organisations.

Summary of main points:

Submission of applications for clinical trials:
A single submission of applications for clinical trials would reduce bureaucracy and ease the workload related to a trial application. Furthermore administrative procedures must be proportionate to the risk of the trial.

Content of Coordinated Assessment Procedure (CAP):
The CAP could be useful for overall assessment of risks vs benefits and Investigational Medicinal Product issues, but would leave local and ethical aspects to be looked at by more appropriate bodies. We support this approach. We do not believe that CAP should be mandatory for all trials, as it is not appropriate for trials that are being conducted only in a single Member State or for later phase trials. A pre-assessment system to evaluate low risk trials is a good idea, as this would reduce the time taken for trials to be approved. However, pre-

[1] Review and refresh of bioscience 2015, published January 2009. http://www.berr.gov.uk/files/file49805.pdf

[2] The NHS European Office was launched in September 2007. It represents the English National Health Service to EU decision-makers. Its role is to inform the NHS of EU affairs and to ensure that the NHS contributes positively to EU developments.

assessment would need to be consistent across Member States, as would decisions on whether trials are 'low risk' or not. Guidance may be required to ensure this.

Non-interventional trials:
The definition of a non-interventional trial should not be broadened as this may impede consistent assessment of trials across the EU, which would stand in the way of harmonisation of clinical trial activity.

Exclusion of academic/ non-commercial sponsors:
Academic or non-commercial sponsors should not be excluded from the Directive, as this would counteract harmonisation measures and could potentially lead to higher risk proposals not being assessed adequately, with consequent implications for patient safety and data validity.

More precise and risk-adapted rules for the content of the application dossier and for safety reporting:
Any clarification and simplification (where appropriate) of the requirements is welcome.

Definition of investigational medicinal products and rules for auxiliary medicinal products:
Clarification with regards the definition of IMPs and rules for the use of auxiliary medicinal products would be useful.

Single Sponsor:
While there should be one single person/ institution ultimately responsible for a trial and its reporting requirements, we maintain our view that co-sponsorship, whereby agreed responsibilities are clearly set out in advance, should be possible.

Emergency Clinical Trials:
The UK has already developed good clinical practice guidelines[3] under the Medical Research Council (MRC) to address the issue of emergency situations, where it is not possible to obtain fully informed written consent. These guidelines state that situations exist where fully informed consent is not possible and in these cases procedures agreed in existing guidelines should be followed, provided favourable ethical opinion is given. These guidelines could be adopted at European level.

Good Clinical Practice in trials performed in third countries:
Trials and data from trials conducted in third countries which relate to medicinal products intended to be used in the EU should not be approved in the European Community if they do not comply with the ethical principles set out in the EU Directive/ Declaration of Helsinki.

[3] Medical Research Council - Guidelines for Good Clinical Practice in Clinical Trials (1998)

Consultation response

Consultation item no. 1:
A single submission would greatly reduce the administrative work of sponsors for submission of documentation to the member states concerned.
Do you agree with this appraisal? Please comment.
Agree
A single submission would not only reduce the administrative burden for sponsors but it would be more flexible than the current system. It would allow each Member State to assess their own local ethical issues, and would also enable overall IMP issues and risk / benefit assessments to be made just once (saving time). Assessment of local issues must remain the remit of Research and development offices (or their equivalent) as these are best placed to assess the suitability of the investigator and site to take part in any trial.

Consultation item no. 2:
A separate assessment would insufficiently address the issue set out above (ie. the assessment would be done by individual member states): The difficulties created by independent assessments would remain.
Do you agree with this appraisal? Please comment.
Agree
Separate assessments would continue to lead to different opinions giving rise to continued difficulties.

Consultation item no. 3:
A central assessment is not appropriate for clinical trials approval and would, not be workable in practice for the reasons outlined in the concept paper.
Do you agree with this appraisal? Please comment.
Agree
A central assessment process would not be practicable as it would not take into account local ethical aspects, and the time taken to arrange committee meetings across the EU would potentially lead to more delays in trials being approved.

Consultation item no. 4:
The Coordinated Assessment Procedure (CAP) could offer a sufficiently flexible approach. It allows for a joint assessment without a cumbersome committee structure. It would allow national practice to be taken into account. It would respect that, as a basic rule, ethical issues clearly fall within the ambit of member states. Is the above catalogue complete?
Is the above catalogue complete?
Yes.
In principle the CAP would offer a sufficiently flexible approach; however variation in the interpretation of the details of the revised Directive by individual Member States may still present barriers and delays.

Consultation item no. 5:
Do you agree to include the aspects under a) and only these aspects, in the scope of the CAP?
Agree.
CAP would be useful for overall assessment of risks vs. benefits and IMP issues, but would leave local and ethical aspects to be looked at by more appropriate bodies, However there must

be flexibility within the revised Directive to allow for the CAP to be reviewed and revised in consultation with stakeholders, as necessary.

Consultation item no. 6:
Disagreement with the assessment report
Which of these approaches is preferable? Please give your reasons.
The 'opt out' would be the most preferable, workable and least burdensome approach, however the phrase "serious risk to public health" is unhelpful and subjective, and should be revised. An alternative phrase could be "contradictory to national clinical practice or legislation".

Consultation item no. 7:
Mandatory/ Optional use of the CAP.
Which of the three approaches described is preferable?
Please give your reasons.
The optional approach is preferable in the first instance and most likely to be supported by academic sponsors. While CAP could be mandatory in all multinational trials, it is not appropriate for trials being conducted only in one Member State area or for later phase trials.

Consultation item no. 8:
Do you think such a pre-assessment is workable?
The UK regulatory authorities have already moved to this approach. Pre-assessment more broadly is theoretically a good idea as it could reduce timescales for approval of low-risk trials. However, pre-assessment needs to be consistent across the EU, as would interpretation of 'risk' in relation to trials. This may prove problematical. Major questions would need to be answered in terms of process and structures for pre-assessment within each Member State in order for the procedure to work successfully. For example, who should carry out pre-trial assessment?

Consultation item no. 9:
Rather than limiting the scope of the CTD through a wider definition of "non-interventional trial", it would be better to come up with harmonised and proportionate requirements which would apply to all clinical trials falling within the scope of the present CTD.
Do you agree with this appraisal? Please comment.
Agree
A proportionate, risk-based approach to clinical trials is vital to a successful revision of the Directive. The approach suggested by the Commission would be a welcome amendment to the Directive.

Consultation item no. 10:
Rather than limiting the scope of the CTD, it would be better to come up with harmonised and proportionate requirements for clinical trials. These proportionate requirements would apply independently of the nature of the sponsor.
Do you agree with this appraisal? Please comment.
Agree
Steps to coordinate requirements with a risk-proportionate approach are welcomed. This would help sponsors to comply with the legislation regardless of whether they are 'commercial' or 'academic/non-commercial' institutions. This approach must take care however, not to limit the development of high quality academic research.

Consultation item no. 11:
More concise and risk-adapted rules for the content of the application dossier and for safety reporting: This approach would help to simplify, clarify and streamline the rules for conducting clinical trials in the EU by providing one, single, EU-wide, risk-adapted set of rules.
Do you agree with this appraisal? Please comment.
Agree
Any clarification and simplification of the rules (where appropriate) would be helpful. However, if and when the Commission chooses to update provisions relating to the content of the clinical trials application dossier and/or safety reporting, this should be done in negotiation with Member State competent authorities and not simply by means of the delegated acts.

Consultation item no. 12:
Are there other key aspects on which more detailed rules are needed?
Patient safety and validity of data are crucial issues to be addressed; however any work carried out by the Commission to provide more detailed rules, should be done so through an appropriate level of dialogue with relevant stakeholders.

Consultation item no. 13:
This combined approached (relating to the definition of' 'investigational medicinal products' and clarifying the rules for auxiliary medicinal products) would help to simplify, clarify and streamline the rules for medicinal products used in the context of a clinical trial.
Do you agree with this appraisal? Please comment.
Agree
There should be standard requirements for those IMPs which are the object of a trial, so a change in the definition of IMPs would be useful. Approvals for the use of auxiliary medicinal products could also subsequently be simplified.

Consultation item no. 14:
Insurance/ Indemnisation: Both policy options could be a viable solution. Which policy option is favourable in view of legal and practical obstacles? What other options could be considered?
Which policy option is favourable in view of legal and practical obstacles? What other options could be considered?
Both options, (removing insurance/ indemnisation requirement s for low-risk trials, or optional indeminsation by Member States) could be implemented as they are not mutually exclusive.

Consultation item no. 15:
Option 1 'maintaining the concept of a single sponsor' may be preferable, provided that 1) it is clarified that the "responsibility" of the sponsor is without prejudice to the (national) rules for liability; and 2) it is ensured that the regulatory framework for clinical trials in the EU is truly harmonised.
Do you agree with this appraisal? Please comment.
While there should be one single person/ institution ultimately responsible for a trial and its reporting requirements, we maintain our view that it should be possible to outsource different responsibilities within a trial to different sponsors. Such shared responsibility would facilitate non-commercial and academic sector engagement in multinational trials as it would help to 'share the load' in terms of works and costs associated with leading a trial.

Consultation item no. 16:
Emergency Clinical trials. The proposals given could be a viable option in order to address this type of research and bring the regulatory framework in line with internationally-agreed texts
Do you agree with this appraisal? Please comment.
Agree
Helpful guidance on this issue already exists in the UK under the MRC GCP[4]. This could be reflected at EU level.

Consultation item no. 17:
In view of the jurisdictional limits, particular consideration should be paid to clinical trials in third countries where the data is submitted in the EU in the framework of the authorisation process of 1) clinical trials; and 2) medicinal products.
Do you agree with this appraisal? Please comment.
Agree
Trials conducted in third countries outside the EU should comply with ethical principles as set out in Directive 2001/20/EC in order to guarantee patient safety and credibility of data. All trials should be registered on the EU clinical trials database.

Consultation item no. 18:
Do you have any comments or additional quantifiable information apart from that set out in the annex to this document?
The success of the revision of the Clinical Trials Directive will depend largely on individual Member States and their interpretation of and adherence to the Directive. The major aim of the revision must be to simplify the Directive where possible and to standardise its implementation within EU Member States. There must continue to be regular revision of the Directive and this should be carried out in negotiation with the national competent authorities and the broader European clinical trials community.

[4] [4] Medical Research Council - Guidelines for Good Clinical Practice in Clinical Trials (1998)