

European Commission: Revision of the 'Clinical Trials Directive' 2001/20/EC concept paper

Response by the Wellcome Trust

May 2011

Introduction

1. The Wellcome Trust urges the European Commission to revise the Directive to develop a harmonised regulatory framework for clinical trials examining the safety and efficacy of medicinal products that is proportionate to the risk posed to trial participants and which will facilitate the conduct of these studies in Europe. The Trust is pleased to be able to respond to the Commission's concept paper on the Revision of the 'Clinical Trials Directive' 2001/20/EC and would urge that the research community is consulted as further details on the proposals are considered (for example, on details of the proportionate approach).
2. In developing this response we have worked closely with the Academy of Medical Sciences (AMS). The Academy is submitting a separate response but our key messages are consistent.
3. Our response highlights the following key points:
 - **Clarifying the scope:** key definitions and appropriate guidance should be revised to ensure that the Directive applies only to trials of the safety and efficacy of medicinal products, as originally intended.
 - **Adopting a proportionate approach:** For trials within the scope of the Directive, a regulatory approach is urgently required where approval and ongoing requirements are proportionate to the risks posed and potential benefits. The research community should be given the opportunity to comment on how levels of risk are categorised and the new system should be piloted, then implemented across all Member States.
 - **A streamlined process for multinational trials:** We support a system of single submission followed by a coordinated assessment procedure for multinational trials. This would aid harmonisation among Member States and ensure consistent application of a new proportionate approach across the EU.
 - **A consistent approach for academic and commercial trials:** We strongly support the application of a revised Directive to both academic and commercial sponsors. However, we suggest that multi-sponsor trials should be permitted under the Directive, since the flexibility this provides will facilitate international collaboration and will promote research translation in a difficult financial climate.
4. It is imperative that the revision of the Directive addresses issues relating to its lack of proportionality throughout clinical trial assessment, authorisation and monitoring. The UK has rigorously implemented the Directive and the day-to-day monitoring by the Medicines and Healthcare Products Regulatory Agency (MHRA) is considered to be more stringent than in other Member States, where implementation is more pragmatic. For more detailed analysis and case-studies of the discrepancy between the UK and other Member States please refer to the Academy of Medical Sciences (AMS) report, 'A new pathway for the regulation and governance of health research'.¹ The UK government has acknowledged that perceived gold-

¹ <http://www.acmedsci.ac.uk/index.php?pid=47&prid=88>

plating of EU legislation is a problem in the UK and it aims to address this as part of its 'Plan for Growth'.²

5. Our response addresses the consultation questions and the heading numbers correspond to the sections in the concept paper.

1. Cooperation in assessing and following up applications for clinical trials

6. Approximately 75 per cent of clinical trials are based within a single Member State. It is important to ensure that any changes to the process for review of multinational trials do not increase the bureaucratic burden and cost to these trials. Studies in a single Member State should apply, as now, to their National Competent Authority (NCA) for robust national approval.
7. For multi-national trials, we support the proposal for a single submission and welcome the outlined proposal for a coordinated assessment procedure (CAP) of the technical aspects of clinical trial authorisation, led by a Reporting Member State. Ethical issues and local aspects related to the suitability of sites, the investigator and national rules should be considered by individual Member States.

1.1 Single submission with separate assessment

A single submission would greatly reduce the administrative work of sponsors for submission of documentation to the Member States concerned. However, the difficulties created by independent assessments would remain (consultation items 1 and 2).

8. We agree that single submission into an 'EU portal' would simplify the system for multinational trials and ensure consistent information requirements across NCAs. Separate assessment by individual NCAs would not address differences in the interpretation of the Directive or reduce the administrative work of sponsors and further steps would be required to harmonise these procedures across Member States.
9. This single 'EU portal' should be aligned, where possible, with successful application systems in individual Member States. The UK's Integrated Research Application System (IRAS),³ has streamlined the application process for all aspects of health and social care research approval applications and provides a good model for a single EU submission for clinical trial authorisation. To promote harmonisation, it is important that the information and documentation required for multinational trials via the 'EU portal' is consistent with that requested by individual Member States for single country trials.

1.2 Single submission with a subsequent central assessment

Central assessment procedure is not appropriate for clinical trials approval because the involvement of all Member States is not needed in most trials, the sheer number of multinational trials conducted every year would make this difficult to implement. Furthermore, central assessment is insufficient to assess the other factors required at a national and local level (consultation item 3).

10. We agree that central assessment by a scientific committee would not be feasible since it is likely that this would delay time to gain authorisation and increase bureaucracy and costs. Furthermore, centralised assessment is not appropriate as national perspectives, such as 'standards of care', differ between Member States and these should be taken into account as part of a risk-based approach to clinical trial authorisation.

1.3 Single submission with a subsequent 'co-ordinated assessment procedure' (CAP)

CAP could offer a sufficiently flexible approach that allows for 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.

² http://cdn.hm-treasury.gov.uk/2011budget_growth.pdf

³ <https://www.myresearchproject.org.uk/SignIn.aspx>

11. The Trust is broadly supportive of the Commission's outlined proposal for a 'co-ordinated assessment procedure' (CAP) for multinational trials, providing this is implemented in such a way as to reduce the time for assessment of clinical trial applications and facilitates a harmonised and proportionate approach across the EU. We would support a proposal for CAP to be taken forward by a single lead 'Reporting Member State', to conduct the assessment based on the technical aspects of clinical trial authorisation (discussed in 1.3.1 Scope of CAP). This assessment would then be shared with all relevant Member States and areas of disagreement could be discussed before reaching the final CAP recommendation. This process should promote harmonisation over time because it would require continuous dialogue between individual NCAs, and remove differences in interpretation of the Directive.
12. CAP must be introduced alongside a proportionate approach to clinical trial authorisations that takes into account the risk posed to trial participants. The implementation of a single joint assessment via CAP provides a crucial opportunity to implement a 'risk-based' approach that is consistent across Member States.
13. We support the CAP procedure in principle but more detail is required on, for example, how the 'Reporting Member State' is selected and how the national and CAP processes will be co-ordinated. For example, we envisage that: both CAP and national procedures could be carried out in parallel to ensure that timescales for application are not increased; and that the CAP recommendation would be considered an EU-wide decision that can be adopted by additional Member States, without further CAP discussion, when new trial sites are added. Further clarification is needed to ensure that once a CAP recommendation has been made, it could be unified with national assessments of ethical and local issues by the relevant NCAs. The NCA would be responsible for issuing the final authorisation to the sponsor(s) from their Member State.

1.3.1 Scope of CAP

Not all aspects of clinical trial authorisation are suitable for CAP – what should be included?

- a) *the risk benefit assessment of the trial including; trial type, design, as well as compliance with manufacturing and clinical practice standards.*
 - b) *ethical aspects*
 - c) *local aspects of judging the suitability of a site for a clinical trial (consultation item 4 and 5).*
14. We agree that only those aspects of risk-benefit assessment listed under 1.3.1a should be included within the scope of CAP and that this aspect of the authorisations process needs to be harmonised across Member States. Ethical aspects of clinical trial assessment listed under 1.3.1b, such as consent and recruitment, should be beyond the scope of CAP and fall within the remit of Member States to take into account differences in national perspectives. We also support the Commission's appraisal that aspects of clinical trial approvals listed under 1.3.1c, relating to the suitability of the trial sites used and the investigator should be carried out by organisations with local expertise. It is vital that there is not duplication in the functions undertaken through CAP and the roles of individual Member States NCAs or Ethics Committees.
 15. National views on ethical issues remain crucial, for example countries can vary widely on views regarding embryonic stem cells and embryo research. Although it is important that Member States continue to carry out independent ethical review, we would encourage interactions between ethics committees between Member States to share best practice and improve efficiency. However, it is vital that any duplication of functions of Ethics Committees and NCAs is avoided.

1.3.2 Disagreement with the assessment report

Disagreement could be resolved by an 'opt out' system, a vote or could be referred to the Commission for an EU level decision (consultation item 6)

16. We would not support the idea of deferring CAP disagreements to the Commission or Agency for a central decision that would be enforced at the EU level, as this would increase bureaucracy and disrupt dialogue between Member States that is important for harmonisation. We propose that the Member States involved in the trial should reach a consensus

recommendation, in a similar process to that currently used in the Voluntary Harmonisation Procedure (VHP). This would mean that the assessment made by the 'Reporting Member State' NCA is passed onto the other NCAs that will be involved in the trial. If there are areas of disagreement these can be discussed by teleconference to be resolved before the final CAP recommendation is made. However, if a Member State believes that the trial poses a 'serious risk to public health or safety of the participant' they should be able to opt out of participation, while other Member States can proceed to conduct the trial if they are satisfied with the assessment.

1.3.3 Mandatory/optional use

CAP could be mandatory for all trials, for all multinational trials or could be an optional process (consultation item 7).

17. CAP should not be mandatory for all clinical trials. This would unnecessarily burden the majority of clinical trials, which occur in only one Member State, by introducing new processes and delays.
18. If CAP is shown to reduce timelines and streamline approvals, the desirable long-term goal would be that all multi-country trials would submit clinical trial assessments via this route. However, we acknowledge that the optional use of CAP will provide the flexibility required for some trials to use different routes to gain authorisation if they are appropriate. CAP will promote the drive for harmonisation of the Directive's implementation across the EU, and will streamline the process of setting up multi-country trials without introducing unnecessary bureaucracy for single-country trials.

1.3.4 Tacit approval and timelines

Under CAP 'tacit approval' is not possible as it requires obligatory authorisation per Member State prior to the trials commencement. Timelines of CAP approvals will be no longer than those provided today by the Directive. It is also suggested that timelines could be shortened when trials pose low risk to participants, where the CAP is more concerned with data reliability. It is suggested these trials ('type-A') trials could be determined by pre-assessment (consultation item 8).

19. We disagree with the Commission's assessment that a system of 'tacit approval' is incompatible with CAP. The 'Reporting Member State' could conduct the assessment, make their recommendation and if no participating Member State NCAs express disagreement with the assessment within a set time, 'tacit approval' could be assumed to avoid unnecessary delay in trial initiation.
20. There should not be any extension to the statutory timescales prescribed by the current Directive. Any increase in authorisation timelines through using the CAP process could decrease Europe's competitiveness in the medical research sector. However, we consider that individual NCAs should remain at liberty to set more ambitious targets for the authorisation of single-country trials.
21. The Clinical Trials Directive was introduced to harmonise procedures during the conduct of trials of investigational medicinal products and steps need to be taken to consolidate and clarify this scope (see section 2.1). Trials of medicinal products can sit at any point on a wide spectrum of risk, from minimally interventional studies where the risks are similar to standard care, to much higher risk studies where far less may be known about the investigational medicinal product. It is important that the regulatory requirements are proportionate to risk and this should be set out in the regulations. Such an approach is applied by the Food and Drug Administration (FDA) in the United States.⁴ Categorisation could be a practical way to implement a risk-based approach, such as that used in the Medical Devices Directive 2007/47/EC.
22. We support the idea of pre-assessment to identify low-risk trials so that the timelines for approval can be reduced for these studies. We agree broadly with the definition of a 'type-A

⁴ <http://www.acmedsci.ac.uk/index.php?pid=47&prid=88> page 48

trial' given in the concept paper, but the term 'insignificant additional risk' will require further specification. The revised Directive will need to ensure that a pre-assessment procedure does not increase bureaucracy and further clarification will be required around who is responsible for assessing whether a trial fits into this category. We suggest that the trial sponsor should be responsible for determining if a trial is low risk, and appropriate support from relevant NCAs will be required to facilitate this process.

23. It is important that a suitable definition of 'type-A' trial is established. The research community should be given the opportunity to comment on how this issue and how levels of risk are categorised across a proportionate approach to the assessment and monitoring of all trials (see section 2.1). Assuming the scope of the Directive is not reduced, we consider that this could include:
- trials that use certain herbal/botanical compounds, vitamins and other substances routinely sold over the counter where there are no known safety issues and the product is to be used at doses similar to those currently used;
 - trials examining treatment optimisation;
 - medicinal products routinely used off-licence; and
 - trials to determine diagnostic accuracy.

2. Better adaptation to practical requirements and a more harmonised, risk-adapted approach to the procedural aspects of clinical trials

Individual Member States have implemented the Directive in divergent ways which has led to inconsistent and divergent practices in approval and ongoing requirements in different Member States.⁵ We would strongly support clarifying the scope of the Clinical Trials Directive to ensure that it is limited, as originally intended, to only trials of medicinal products.

2.1 Limiting the scope of the Clinical Trials Directive

2.1.1 Enlarging the definition of non-interventional trials

Rather than limiting the scope of the Directive by widening the definition of 'non-interventional trial' it would be better to have harmonised and proportionate requirements which would apply to all clinical trials falling within the scope of the present Directive (consultation item 9).

24. Since Member States have implemented the Directive in different ways, the level to which requirements are standardised will be key to improving the environment for conduct of clinical trials in the future. However, it should be recognised that this may require rewording and clarification of definitions within the Directive. Current problems with the Directive, demonstrated by the case study in box 1, include:
- strict interpretation of the definitions in Article 2, particularly of 'non-interventional trials' makes the scope of the Directive very broad;
 - the broad scope of the Directive is exacerbated by a one-size-fits-all approach, which results in costly delays to trials which pose little risk to participants; and
 - inconsistent interpretation of both the authorisation and ongoing requirements for clinical trials.

Box 1: Case study on the impact of the broad scope of the Directive

We understand that some studies in the UK have been seriously impeded because they were considered to be interventional trials. For example, a study that aimed to determine the optimal arterial oxygen saturation in pre-term infants was classed as an interventional clinical trial despite the fact that oxygen is routinely used at the tested concentrations in clinical practice.⁶ This study was then required to be good clinical practice (GCP) and good manufacturing practice (GMP) compliant, which are burdensome to implement. Further examples are provided in the AMS report.⁷

⁵ <http://www.acmedsci.ac.uk/index.php?pid=47&prid=88> page 44

⁶ <http://www.acmedsci.ac.uk/index.php?pid=47&prid=88> page 48

⁷ <http://www.acmedsci.ac.uk/index.php?pid=47&prid=88> pages 48-49

25. We strongly support clarifying the scope of the Directive to ensure it is limited to trials examining the safety and efficacy of medicinal products. All other types of trial should remain outside the scope of the Directive and individual Member States should be responsible for overseeing these trials, as they do for other types of clinical research. In the UK, clinical research is adequately overseen by the robust regulation and governance framework provided by research ethics committees and other organisations.
26. The scope of the Directive can be refined and restricted through clarification of definitions within the Directive. We disagree with the Commission's proposal that the definition of 'non-interventional trials' should remain unchanged. The definition of non-interventional trials at article 2c should be clarified, to address the most problematic part of the current definition and interpretation that has led to the inclusion of studies that include additional diagnostic and monitoring procedures, which rarely add additional risk (see box 2). Some countries have already gone further to limit and clarify the scope of the Directive, for example, in the Netherlands where the definition of non-interventional trials was not transposed into national law. In addition to clarifying exclusion from the Directive at article 2c, this should be complemented by further clarification of the definition of 'clinical trial' at article 2a.

Box 2: Scope of the Directive - diagnostic and monitoring procedures

The current definition of 'non-interventional trial' means that the scope of the Directive is very broad. A hypothetical example shows how the addition of an intervention can determine whether a study is regulated under the Directive according to current definitions. In a study looking at a side effect of a vaccine that requires taking cerebrospinal fluid from patients:

- If the vaccine is administered within the terms of its marketing authorisation as part of usual clinical practice, then it would not be subject to the requirements of the Directive.
- However, if researchers want to take cerebrospinal fluid from patients that will be given the vaccine within the terms of its marketing authorisation, this intervention means that the study would be now deemed a clinical trial of an investigational medicinal product. The study must fulfil the requirements of the Directive.
- If cerebrospinal fluid is taken for an unrelated study in which patients are not receiving a medicinal product, this would not be regulated under the Directive. In the UK such a study would be regulated through other mechanisms.

This example illustrates that it is not logical to determine the scope of the Directive according to the addition of an intervention because it is the use of a medicinal product, not the additional intervention, that needs to be regulated through the Directive.

27. We would strongly recommend that the ongoing revision of Directive must not increase the range of trials which fall within its scope. It is a priority that the scope of the Directive is clarified (see paragraph 26) and a proportionate approach to trials of medicinal products is piloted and implemented to alleviate unnecessary burdens on low risk trials. Once this has been achieved, in the longer term, there may be value in looking at ways to harmonise regulatory approaches to trials outside the scope of the Directive, but we do not consider this to be desirable in this phase of revision.

2.1.2 Excluding clinical trials by 'academic/non-commercial sponsors' from the scope of the Clinical Trials Directive

Rather than limiting the scope of the Directive by excluding academic sponsors it would be better to have harmonised and proportionate requirements which would apply to both academic and commercial sponsors (consultation item 10).

28. We agree with the appraisal that academic sponsors should not be excluded from the scope of the Directive, which should continue to apply to both academic/non-commercial and commercial sponsors. Not all academic trials are low risk and it is important to provide adequate protection to participants. This is also fundamental to facilitating collaborations

between academia and industry throughout Europe, a key priority in the EU green paper on the common strategic framework for EU research and innovation.⁸ It is essential for the health of the EU biosciences sector that collaboration between academia and industry is promoted, and therefore consistency in approach and promotion of best practice should be supported.

29. The Impact on Clinical Research of European Legislation (ICREL) project report shows that academic trials have been disproportionately affected by the Directive, largely because academic sponsors have less resource and infrastructure to navigate the bureaucratic challenge associated with the Directive.⁹ However, we acknowledge that measures to increase proportionality as part of the revision of the Directive should address many of the issues that have been detrimental to the conduct of academic trials.

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

The rules on the content of the application dossier and safety reporting have been cited as areas needing greater harmonisation and risk-adaptation. This could be addressed by providing detailed guidance on these subjects as Annexes to the legal act (consultation item 11).

30. We would strongly support measures to implement a risk-based approach, with clear guidelines and an appropriate assessment system. Consideration needs to be given to the specific requirements for trials of differing risk, for example in relation to intensity of auditing, monitoring, safety reporting and insurance. The objective should be to significantly decrease the burden on trials of low risk, particularly for those studies whose risk is similar to 'usual care'.¹⁰ Examples of requirements that need a risk-based approach, greater clarity and guidance are safety reporting and good clinical practice (GCP).
31. The research community should be given the opportunity to comment on how levels of risk are categorised across a proportionate approach to the assessment and monitoring of all trials. A proportionate approach in clinical trial approval and monitoring should take into account:
- the risk posed to a participant in the study compared to standard care, for example a high risk is likely to be associated with a first in human study, versus a study looking at treatment optimisation that will not differ significantly from routine clinical practice. This risk assessment will include factors such as the extent of knowledge and prior use of the IMP and the known or suspected risks.
 - the risk to the sponsor, institutions, and the health service;
 - the risk to broader public health posed from not conducting the research; and
 - the potential benefits of the trial. The benefit-risk balance will differ significantly between the populations involved. For example, a patient suffering from a life-threatening disease may be prepared to accept greater risk, than a healthy volunteer, to participate in a trial.
32. The safety reporting requirements for clinical trials, including those for suspected unexpected serious adverse reactions (SUSARs), currently result in unnecessary duplication. For example, currently both NCAs and Ethics Committees receive SUSAR reports, but Ethics Committees do not act on this information. The concept paper does not describe how these reporting requirements will be simplified. We recommend that the revised Directive clarifies that NCAs are the primary stakeholder of information relating to safety reporting and should receive routine reports, while Ethics Committees should receive the appropriate summary information needed to fulfil their function.
33. How harmonisation of a risk-based approach will be achieved is not outlined or discussed in the concept paper. It is essential that a risk-based approach is piloted and evaluated before its implementation. The MHRA and Medical Research Council have developed guidelines in the UK that are currently being trialled and could be used to inform methods of a risk-based

⁸<http://europa.eu/rapid/pressReleasesAction.do?reference=MEMO/11/76&format=HTML&aged=0&language=EN&guiLanguage=en>

⁹ http://www.efgcp.be/downloads/icrel_docs/Final_report_ICREL.pdf

¹⁰ <http://www.acmedsci.ac.uk/index.php?pid=47&prid=88> page 51

approach in the EU.¹¹ Although we welcome the use of Annexes to provide more information and guidance, we are concerned that this will be insufficient for true harmonisation. Detail is lacking on how the guidance will be implemented at the level of Member States.

34. The Trust is concerned that the concept paper draws attention to the International Conference on Harmonisation guidelines on good clinical practice (ICH-GCP) without acknowledging that these guidelines are not appropriate for all types of trials. ICH-GCP was developed in 1996 by the pharmaceutical industry to facilitate multinational trials but these standards are less relevant, and often difficult to apply, to trials in non-commercial settings. This has been acknowledged in the UK where ICH-GCP is not a legal requirement. It is essential that GCP requirements are clear and proportionate to risk. For example, in the UK there is a lack of clarity around which staff members need GCP training for low risk non-commercial trials; would every member of nursing staff need to be GCP trained if they are administering a low risk intervention to newborn babies? This issue would benefit from clarification and it is important that the resulting requirement is proportionate to the risks involved.

Are there other key aspects which require detailed rules? (consultation item 12)

35. In our previous response UK academics identified that the definition of 'extemporaneous preparation' required clarification, as well as what constitutes a 'substantial amendment' to the terms of the application or trial protocol.¹²

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

The uncertainties and lack of a proportionate approach to determining investigational medicinal product (IMP) and non-IMP in clinical trials have caused major problems in multinational trials. A combined approach to clarify the definition of an IMP and to introduce a new term, the 'auxiliary medicinal product', could simplify the Directive (consultation item 13).

36. In principle the Trust would support the introduction of the notion of 'auxiliary medicinal products', although we would like more information of what 'proportionate regulatory regime' they would be subjected to.
37. We are concerned with the new proposed definition of an Investigational Medicinal Product given as a medicinal product 'which is being tested or used as a reference in a clinical trial'. If the product is being used 'as a reference' in the trial it should not be classed as an IMP because it often will follow the current standard of care, and therefore, should be classed as an 'auxiliary medicinal product'.

2.4 Insurance/indemnisation

The Directive does not discriminate insurance requirements for trials on the basis of risk. This could be addressed by removing insurance/indemnisation requirements from low-risk trials or obligating Member States to provide indemnisation for trials conducted in their territory (consultation item 14).

38. This section is not clear on the problems the proposed options are trying to address and more information and clarity is needed on both of the options outlined. Removing insurance requirements from low risk trials would be consistent with a broader proportionate approach to clinical trial authorisation and monitoring. This would need to be flexible to accommodate the whole range of clinical trials. The Commission should outline whether Member State indemnification for clinical trials would be obligatory or optional; whether Member State indemnification would also apply to commercially sponsored trials; and how this would be funded. So whilst we do not disagree with these suggestions in principle, equally we do not fully understand them and feel they need greater investigation and clarity.

¹¹ <http://www.mhra.gov.uk/Howweregulate/Medicines/Medicinesregulatorynews/CON114358>

¹² http://www.wellcome.ac.uk/stellent/groups/corporatesite/%40policy_communications/documents/web_document/WTX058237.PDF

2.5 Single sponsor

The Directive is based on the concept of a single sponsor but it is considered that this has made multinational trials difficult. An alternative could be to allow multiple sponsors where each sponsor is responsible for a specific task or conduct in a particular Member State. (consultation item 15).

39. We are pleased that the Commission recognises the distinction between liability and responsibility. However we do not support the concept that single sponsorship should be maintained in its current form. Harmonisation is important but multi-sponsorship does not hinder harmonisation.
40. Trials may involve more than one organisation who will wish to share responsibilities for the trial through sponsorship, and this needs to be recognised by the Directive. We propose that the Directive should be revised to accommodate multi-sponsor trials. Under the current system the concept of a single sponsor has prevented the conduct of clinical trials between EU Member States because the sponsorship from one Member State has not been accepted by other Member States (box 3). A system of multi-sponsorship has been used successfully within the UK and this could be used as a framework for implementation within and between other Member States. Furthermore, multiple sponsors should facilitate collaboration with non-EU countries since, for example, European Member States cannot act as sponsors for trials in the US.

Box 3: Case study on the need for co-sponsorship

We understand that in one multi-country trial where a UK University was acting as sponsor, other Member State NCAs were insisting on joint sponsorship. However, the University interpreted the Directive to mean that there had to be a single sponsor. Since, the University refused to accept co-sponsorship the trial was unable to go ahead in the other Member States and as a consequence of these problems, it was decided to recruit patients from additional trial centres outside Europe.

2.6 Emergency clinical trials

The Commission outlines provisions to take into account that informed consent and information from an investigator can take place after or during a trial in certain circumstances. This will facilitate emergency clinical trials under the Directive (consultation item 16).

41. The UK Medicines for Human Use (Clinical Trials) Regulations were amended in 2006 to set out conditions under which it was appropriate for emergency clinical trials to take place.^{13,14} We consider that this amendment has succeeded in resolving the difficult balance between the protection of individuals and maintaining a facilitative environment for research. The Commission's proposals are consistent with the current UK regulations and we support the wider adoption of this approach.

3 Ensuring compliance with good clinical practices in clinical trials performed in third countries

Consideration is given to clinical trials in third countries where the data will be used in EU authorisation. The concept paper suggests codifying the legislative framework to help implementation of the Directive (2.7.2.4); supporting capacity building in third countries where the regulatory framework is weak; and suggest registering all trials in third countries if they are to be used in marketing authorisations in the EU (consultation item 17).

42. We welcome the Commission's recognition of the difference between clinical trials in low and middle income countries where the data generated is to be used in EU marketing authorisation,

¹³ Medicines for Human Use (Clinical Trials) (Amendment No. 2) Regulations 2006: <http://www.legislation.gov.uk/ukxi/2006/2984/introduction/made?view=plain>

¹⁴ National Research Ethics Service (2008) *Informed Consent in Clinical Trials* pp8-9 <http://www.nres.npsa.nhs.uk/applications/guidance/clinical-trials/?entryid62=66934>

and where it is not. This is important because there are likely to be differences in the evaluation of risks and benefits of a particular intervention between different countries. The Trust funds clinical trials in low and middle income countries where the interventions trialled are to be used in those countries, rather than where the data is to be used in EU marketing authorisation, and we agree that there should not be an increase in burden or EU scrutiny for trials of this type. However, it is also important that any changes to the regulation of clinical trials in third countries do not inadvertently impact on trials where the data will not be used for EU marketing authorisation.

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