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British Heart Foundation response to European Commission consultation on the 'Assessment of the Functioning of the Clinical Trials Directive' 2001/20/EC

Introduction

The British Heart Foundation (BHF) is the nation's heart charity and the largest funder of cardiovascular research in the UK. We fund more than half of all university-based cardiovascular research in the UK, with BHF-funded researchers and projects at centres in over 30 cities across the UK. Between April 2008 and March 2009 we invested over £145 in cardiovascular research every minute – a total annual investment of over £78 million, of which around £5 million funded controlled clinical trials.

Our research portfolio extends from fundamental laboratory-based molecular, biological and genetic studies to large scale clinical trials of novel and existing preventive and therapeutic interventions. Clinical trials are paramount to ensuring data on the safety and efficacy of new treatments or devices are rigorously collected, enabling patients with a range of diseases including cardiovascular disease to benefit from medical innovation.

The adoption of the Clinical Trials Directive across the EU has helped to simplify and harmonise some of the administrative requirements for clinical trials within the EU. However, the legislation has had a number of **unintended consequences that have made it more difficult for BHF researchers to conduct clinical trials**. Some of our researchers have also indicated in response to a qualitative survey that **regulation and administration have constrained their ability to carry out research, and provided a disincentive to continuing a research career**. The BHF therefore welcomes the opportunity to respond to this consultation, and the Commission's decision to seek to address the concerns within the clinical research community.

This response draws on expertise from a number of BHF cardiovascular clinical researchers, who have had direct experience of the operation of the Directive since its introduction.

The BHF is a member of the Association of Medical Research Charities, a stakeholder association of the leading medical and health research charities in the UK, and we support their response to this consultation.

Streamlining the NCA and REC authorisation processes

The present system requires that for multinational clinical trials, a separate Clinical Trials Authorisation (CTA) must be obtained by the National Competent Authority (NCA) of each Member State in which the trial takes place. Though the Directive aimed to set common rules for authorisation of a trial within Europe, the reality in practice has seen an inconsistent application of rules between NCAs. An example provided by a BHF Chair of Cardiology highlighted this issue, whereby a trial running in France was unable to add a site in the UK due to it requiring NCA approval in the UK – in contrast, it had not required NCA approval within France.

Streamlining the NCA authorisation process would be a progressive step towards ensuring greater consistency between Member States, reducing the capacity for inconsistent application of the authorisation rules between different NCAs. Closer dialogue between NCAs resulting in a single decision whether to authorise the trial in participating Member States, or an authorisation from one body that would apply across all Member States (as mentioned in 3.3.2), could enable this to take place.

Avoiding duplication of work across Member States is also important with regards to Research Ethics Committee (EC) authorisation, and a similar one-stop option for ethics approval, or greater cooperation between ECs, could help to reduce this duplication of administrative work. Independent ethics review is a vital requirement to ensure that the rights, safety and wellbeing of participants are protected. We have received positive feedback on the service from the UK's research ethics committees, and the Integrated Research Application System has already helped to reduce the amount of duplication involved in applications for approval within the UK. One CTA application dossier, which could be centrally placed and accessible to all NCAs and ECs, could have a similar impact in reducing the complexity of the approval process.

Reducing inconsistencies in interpretation of the Directive

Inconsistent application of the Directive has resulted in differences between Member States in the interpretation of what constitutes a substantial amendment. As a result, there has been some over-classification in the notification of substantial amendments to NCAs, as highlighted in 4.1.1 of the consultation document, which has led to a significant increase in the number of amendments submitted since the Directive was implemented. We believe that clarification is needed to ensure that substantial amendments are interpreted consistently across the EU, and are limited to those amendments that genuinely impact on issues such as patient safety. Under the present Directive for example, the addition of a new site to an approved trial, not listed in the original application, constitutes a substantial amendment and must undergo ethical review – we believe that consideration should be given in any review of the current legislation as to whether this can be reclassified.

Similarly, reports of Suspected Unexpected Severe Adverse Reactions (SUSARs) have seen a substantial increase since implementation of the Directive, and we agree with the

issues identified in the consultation document. The BHF believes that further clarification is needed to address how SUSAR reports are used, to ensure that patients are appropriately protected.

There are also inconsistencies with regards to interpretations of interventional and non-interventional trials, with researchers informing us of issues both within and between Member States. One trial may be considered interventional in one Member State, and non-interventional in another, depending on their interpretation of the Directive. Greater clarity is needed in order to avoid confusion and minimise inconsistencies in this area.

While adopting the Directive's text in the form of a Regulation could address issues of inconsistencies experienced through transposition, it may be more feasible to achieve this through a review of the existing implementing guidelines. We believe that the Commission should act swiftly to ensure that these issues are addressed.

Regulating clinical trials according to risk

The current legislation does not discriminate between trials of varying levels of risk. Some of our researchers have seen examples where higher risk non-interventional trials, such as those examining physiology rather than treatment efficacy or safety, have taken place without compliance with the legislation, in contrast to some lower risk interventional trials. The assumption in 4.1.3 of the consultation document that non-interventional trials typically have a lower risk than interventional trials and as such are excluded from the Directive is therefore debatable. Patient safety should be of paramount consideration throughout the approval process, and this can be taken into account according to the risk posed to the patient by a particular trial. We believe that adopting a risk-based approach to regulating clinical trials, as proposed by the European Medical Research Councils (EMRC) foresight study on 'Investigator-Driven Clinical Trials' (IDCT), would provide a clearer, fairer system for approval. Determination of risk could be attributed by the NCA in consultation with the sponsor and/or EC.

Making the system more practical for academic sponsors

The requirement for trials to have a single sponsor for the application continues to provide practical difficulties for academic sponsors. As highlighted in 5.2.2, it is difficult for an academic sponsor to hold the responsibility for clinical trials performed in another Member State, particularly when there have been differences in the way the Directive has been implemented. This issue should be reviewed to investigate the possibility of allowing co-sponsorship in situations where this may help to improve efficiency of the trial.

We are concerned by the proposal in 5.4.3 to exclude clinical trials of academic sponsors from the scope of the Directive. Reviewing the Directive to take account of experiences within academia would be beneficial, but a comprehensive exclusion of all trials of academic sponsors would be far too restrictive. Under this proposal, no academic trial could be used for the application of a marketing authorisation in the EU, with any new discoveries within

academia requiring commercial sponsors to take them forward – this would have a damaging effect on academia and research.

Facilitating clinical trials in emergency situations

In its current form, the Directive does not sufficiently address the issue of consent for clinical trials in emergency situations, in situations such as myocardial infarction where it may not be feasible to obtain informed consent from the patient. Since the Directive was transposed, the UK has legislated to allow clinical trials in emergency situations, with many other Member States similarly amending their own legislation. As a result, there are divergent standards for good clinical practices within emergency trials. Any review of the Directive should seek to ensure that emergency trials can take place while ensuring protection of patients and consistency across the EU.

Conclusion

- There are a number of positive elements of the Directive, but greater consistency between Member States is needed to ensure that the legislation works effectively.
- Streamlining both the NCA authorisation and ethics approval processes would be progressive steps towards ensuring greater consistency between Member States.
- Clarification on substantial amendments and SUSARs is needed to ensure that they are interpreted consistently across the EU.
- Adopting a risk-based approach to regulating clinical trials would provide a clearer, fairer system for approval.
- A comprehensive exclusion of all trials of academic sponsors from the Directive would be far too restrictive and would have a damaging effect on academia and research.
- Any review of the Directive should seek to ensure that emergency trials can take place while ensuring protection of patients and consistency across the EU.
- This consultation has provided an excellent opportunity to address the inconsistencies identified, which we hope will be fully taken by the Commission when considering its response.
- If you would like further information about this response, please contact Joseph Clift, Policy Officer, on cliftj@bhf.org.uk or +44 207 554 0156. We would be happy to discuss any of these issues further with the Commission.

Kind regards,

Professor Peter Weissberg
Medical Director
British Heart Foundation