European Commission consultation on the concept paper on the revision of the Clinical Trials Directive 2001/20/EC

Response from the British Heart Foundation

Summary

- An 'EU portal' administered by the European Medicines Agency could ensure consistency and a reduced administrative burden for single submissions
- A 'co-ordinated assessment procedure' could be beneficial for multinational trials
- A proportionate approach would help to address the problems that trials currently suffer from the Directive's one-size-fits-all approach
- Academic trials should not be excluded from the scope of the Directive, and would benefit from a move to co-sponsorship
- Provision for emergency trials should be explicitly defined within the Directive

Background

The British Heart Foundation (BHF) is the nation's heart charity. We fund more than half of all non-commercial cardiovascular research in the UK, with BHF-funded researchers and projects at centres in over 30 cities across the UK. Over the past 3 years we have invested around £200 million in cardiovascular research. We estimate that we fund over £5 million of controlled clinical trials per year.

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 medical devices are rigorously collected, enabling patients with a range of diseases including cardiovascular disease to benefit from medical innovation.

The unintended consequences resulting from the Clinical Trials Directive and its implementation 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 in 2009 that regulation and administration have constrained their ability to carry out research, and provided a disincentive to continuing a research career. We therefore welcome this opportunity to respond to the Commission's concept paper on revising the Directive.

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. We also support the response from the Academy of Medical Sciences to this consultation.

Single submission process

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 National Competent Authorities (NCAs). A BHF Chair of Cardiology highlighted an example where inconsistencies in different Member States over interpretation of the Directive led to a trial not taking place in the UK. The ARCH trial (Aortic Arch Related Cerebral Hazard), which was already running in France, was found under the UK interpretation of the Directive to require approval from the MHRA. In contrast, approval had not been needed from France's NCA due to their interpretation of the same Directive. This issue ultimately resulted in the UK site, and the 100 patients that would have been recruited, not participating in the trial.

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. We agree with the Commission's proposal to create an 'EU portal' administered by the European Medicines Agency (EMA), which should ensure that requirements are consistent between different Member States. This should also reduce the administrative burden by avoiding unnecessary duplication across Member States. The Integrated Research Application System has already helped to reduce the amount of duplication involved in applications for approval within the UK, and this could provide the EMA with a useful model.

In terms of assessment, we agree that separate assessments of information independently by each Member State would not address the inconsistent application of the Directive's requirements. Central assessment by a scientific committee made up of Member States representatives would be impractical for the reasons stated in the concept paper, and could lead to an increase in administration and a loss of national perspectives.

Provided that it would not add to the cost or the bureaucratic burden for researchers, and adopts a proportionate approach, we would support the Commission's proposal for a **single submission with a subsequent 'co-ordinated assessment procedure' (CAP)**. This would enable all Member States involved in a multinational trial to input to the application's assessment of the aspects covered in 1.3.1 (Scope of the CAP), led by a single 'Reporting Member State'.

We agree with the Commission that the CAP should cover those aspects of risk-benefit assessment covered in 1.3.1a. We also agree that the CAP should not cover the issues related to ethical issues or to local expertise, as outlined in 1.3.1a and 1.3.1b – these should remain the responsibility of the NCA.

In terms of **resolving disagreement** about the assessment conducted by the CAP, referral to the Commission or EMA could increase bureaucracy. A process should be put in place to ensure that Member States can seek to resolve disagreement, with an option for a Member State to opt out of the trial if they consider there is a serious risk to public health or participant safety.

We hope that the CAP will enable harmonisation of the Directive within Member States, and see benefits to its use for multinational trials, but do not believe this should be applied to all trials as suggested in 1.3.3. This could result in further bureaucracy for single-country trials. The Commission should pilot use of the CAP for multinational trials before considering whether to make this mandatory for all multinational trials.

We agree that the timelines for the CAP should be shortened for those trials considered to be 'low-risk' to trial participants ('type-A trials'). However, it is crucial that this type of trial be clearly defined in order to avoid some of the problems experience with inconsistent implementation of the Directive. The revision of the Directive should have, as a central aim, speeding up the approval processes for trials – the CAP should be a mechanism that reduces, rather than adds to, the time currently taken for a trial to be approved.

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

The current Directive has been ineffective in discriminating between trials of varying levels of risk. Many 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 one-size-fits-all approach currently applied by the Directive is not fit-for-purpose, and has exacerbated the problems associated with the Directive's broad scope. A report from the Academy of Medical Sciences in January 2011 highlights a number of examples where a lack of a proportionate approach has been shown to be problematic.[1]

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 **proportionate approach** to regulating clinical trials would provide a clearer, fairer system for approval.

Further clarification should be provided on the scope of the Directive to ensure that this is limited to trials examining the safety and efficacy of medicinal interventions. All remaining trials should be the responsibility of individual Member States. Clarification in particular should be provided for the definition of 'non-interventional trials', which has led to the broad scope of the Directive. This, coupled with a proportionate approach, will help to reduce the bureaucratic burden on low-risk trials.

We agree with the Commission that trials conducted by **academic sponsors** should not be excluded from the scope of the Directive. A comprehensive exclusion of all trials of academic sponsors would be far too restrictive. Under such a 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.

[1] Academy of Medical Sciences (2011) A new pathway for the regulation and governance of health research

We support risk-adapting the rules for the content of the application dossier and for safety reporting, and ensuring these are more precise should enable further harmonisation. It is important that the research community is fully involved in the process of categorising the level of risk in the context of the revised Directive's proportionate approach. 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. A current for example, concerns the addition of a new site to an approved trial, not listed in the original application, which under the current interpretation constitutes a substantial amendment and must undergo ethical review.

Single sponsorship

We are disappointed that despite recognising many of the problems associated with single sponsorship for trials, the Commission is reluctant to move to a system of shared sponsorship. The requirement for trials to have a single sponsor for the application continues to provide practical difficulties for academic sponsors. 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. Co-sponsorship could help to improve efficiency of the trial, and we believe the Commission should give greater consideration to departing from single sponsorship.

Emergency clinical trials

At present, 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.

We welcome the Commission's recognition of this gap in the current Directive, and agree with the proposal in 2.6 to amend the Directive to encompass the internationally agreed texts that explicitly address emergency trials.

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.

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