



## Revision of the EU Clinical Trials Directive

*A joint statement from non-commercial research organisations in the UK*

**We welcome the proposal to revise the EU Clinical Trials Directive. We call on the EU institutions, national Governments and others to develop a supportive environment for conducting clinical trials, enabling development and testing of treatment options for patients. Revisions should focus on reducing bureaucracy, which acts as a disincentive to setting up clinical trials. This revision should include streamlining authorisation processes; adoption of a proportionate approach to the regulation of clinical trials; and the provision of clearer guidance.**

### **What are clinical trials?**

We invest in research with the goal of developing treatments. All potential new treatments begin in the laboratory but then we need to find out how well they work in patients. We do this through clinical trials. These are controlled tests that aim to establish how well a drug works ('efficacy') and how safe it is. Clinical trials are a vital stage in the drug development process: without clinical trials we would not know which treatments are most effective for patients.

### **How are clinical trials governed?**

Under the Clinical Trials Directive 2001/20/EC (CTD), all clinical trials investigating the safety or efficacy of a medicinal product in humans must meet a number of legal obligations. In the UK, the CTD was transposed into national law as the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), which came into force on 1<sup>st</sup> May 2004.

The CTD provides a standardised framework which sets out how clinical trials investigating the safety or efficacy of a medicinal product in humans must be conducted throughout the European Union (EU). The scope of the Directive includes medicinal trials with healthy volunteers and small scale or pilot studies. When introduced, the aims of the Directive were to:

- Protect subjects participating in clinical trials
- Ensure quality of conduct
- Harmonise regulation and conduct of clinical trials throughout Europe

It has been widely acknowledged that the last of these aims has not been met. In addition, there has been no evidence to that the increased bureaucracy resulting from the Directive has improved patient safety.

### **What has been the impact of the CTD?**

There have been concerns about the way the Directive has been implemented and how effective it has been.

The Directive has had the following negative impacts on clinical trials:

1. Divergent application, largely due to inconsistent interpretation of the Directive across different Member States, has made it increasingly difficult to undertake multi-national clinical trials.
2. The Directive has led to a greater administrative burden (with associated costs and delays) for clinical trials. The assessment undertaken by the Impact on Clinical Research of European Legislation (ICREL)<sup>1</sup> found that non-commercial sponsors required an increase from 1.5 to 2.8 FTE (full-time equivalent) staff to manage administrative tasks associated with a Clinical Trial Authorisation, and that there was an increase in time between finalisation of protocol and first patient recruited from 144 to 178 days.
3. The 'one size fits all' regulatory requirements mean that trials on well-understood drugs are regulated in the same way as trials of completely new drugs, where the risks are unknown. This has increased the difficulties in conducting low-risk clinical trials.

The European Commission announced on 10<sup>th</sup> December 2008 that an assessment would be made of the application and impact of the CTD. This assessment is considering various options for improving the functioning of the CTD with a view to making legislative proposals in the first half of 2012. To further inform these proposals, in February 2011 the Commission published a concept paper which sets out their 'preliminary appraisals' of policy options for revising the CTD.

#### **What do we want to improve?**

We would like to see revision to the Directive and the accompanying guidance in the following areas:

***Proportionate approach:*** A proportionate approach to the assessment and regulatory requirements of clinical trials examining the safety or efficacy of medical products should be introduced, ideally with the onus on the Sponsor to justify the assessment. This should take into account a number of factors including the extent of prior knowledge and experience with the Investigational Medicinal Product (IMP) and the patient population involved.

***Greater clarity on the scope of the Directive:*** It is essential that the scope of the Directive is clarified to ensure it is limited to trials examining the safety and efficacy of medicinal products as originally intended and that it is applied in the same way across Member States. The lack of clarity of the definitions included in the Directive contributes to its inconsistent implementation across Member States. Where the regulatory requirements are unclear there is evidence that those undertaking trials go above and beyond the requirements to ensure that they are compliant. The definitions that in the Directive should be revised to ensure the scope of the Directive is clear and that studies are treated consistently across Member States.

***Streamlined authorisation and assessment of clinical trials:*** We are broadly supportive of the approach outlined in the recent concept paper from the Commission on having a single 'EU portal' for submitting documentation for multi-national trials. It could reduce the administrative burden of multiple submissions at the time of initial application as well as amendment and clinical study reporting.

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<sup>1</sup> [http://www.efgcp.be/downloads/icrel\\_docs/Final\\_report\\_ICREL.pdf](http://www.efgcp.be/downloads/icrel_docs/Final_report_ICREL.pdf)

However, we would like to see a full impact assessment to be reassured that this proposal would not lead to increased cost or approval times. We are supportive of the principle behind the proposal for a 'coordinated assessment procedure' (CAP) that would allow all Member States to input into application assessments but would have a lead 'Reporting Member State'. However, until there is more detail as to how this would operate in practice, it is difficult to be strongly supportive of the proposal. Such detail should include how a proportionate approach would be harmonised across Member States. Without this information, it is difficult to appraise whether this would lead to improvements in setting up multinational studies.

***Simplified approval and monitoring requirements:*** The Directive sets out specific requirements for safety reporting for clinical trials including reporting all suspected unexpected serious adverse reactions (SUSARs) to the National Competent Authority (the MHRA<sup>2</sup> in the UK), the main research ethics committee and the national competent authorities of any other Member State where the trial is being conducted. Sponsors are also required to submit an annual safety report to both the National Competent Authority and relevant ethics committees. These arrangements lead to unnecessary duplication, without enhancing patient safety. The Commission's concept paper has not identified how these requirements could be revised and we would like greater clarity on how these arrangements could be simplified.

***Clearer, more detailed guidance:*** We would welcome clearer and more detailed guidance in a number of areas to improve understanding of the Directive. The recent proposals for updating the guidance on the current requirements for reporting suspected adverse serious adverse reactions (SUSARs) were welcomed. In addition to this, there is a need for additional clarification on other issues, such as what constitutes a 'substantial amendment' to a study protocol.

***Inclusion in the CTD for academic sponsors:*** We agree with the appraisal outlined in the Commission's concept paper that clinical trials by 'academic/non-commercial sponsors' should not be excluded from the scope of the Directive.

### Case studies

#### **Arthritis Research UK**

In 2004, Arthritis Research UK funded a study looking at the effect of Vitamin D on older people with knee osteoarthritis. Vitamin D was classed as an investigational medicinal product under the CTD, and so researchers had to pay an additional £70,000 to have the vitamin 'repacked'. At the same time, the vitamin could be bought across the EU from online health stores, where it was deemed safe for anyone to buy and use. The requirements in the Directive increased the cost of the research with no impact on the safety of patients. The current revision of the CTD does not do enough to encourage regulatory authorities to take a risk-based approach, preventing similar cases in the future.

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<sup>2</sup> Medicines and Healthcare products Regulatory Agency (MHRA)

### **British Heart Foundation**

A Chair of Cardiology funded by the British Heart Foundation (BHF) 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 National Competent Authority owing 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.

### **Cancer Research UK**

EuroNet-PHL-C1 is a trial for children and young people under 18 years old, comparing different ways of treating Hodgkin's lymphoma to help lower the risk of long-term side effects. Doctors usually treat Hodgkin's lymphoma with a combination of chemotherapy drugs (including procarbazine and dacarbazine), and many people have radiotherapy after chemotherapy.

The aims of this trial are to see if chemotherapy alone is as good as chemotherapy and radiotherapy for some people with Hodgkin's lymphoma; to see whether dacarbazine is as good as procarbazine; and to look at the long term effects of these drugs on fertility.

For this trial, the number of Investigational Medicinal Products (IMPs) included on the Clinical Trials Authorisation (CTA) in different Member States varies from as many as 14 to as few as two. This clearly demonstrates the lack of common understanding of the definition of an IMP by National Competent Authorities and researchers. The EU guidance document "Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials" has not resolved this issue.

### **Paediatric trial**

The recent Academy of Medical Sciences report on the regulation and governance of health research in the UK highlighted an example where the Directive increased the burden in terms of resource in setting up a trial due to its 'one size fits all' requirements. A trial in pre-term babies is aiming to establish the optimum arterial oxygen saturation, which is currently not standardised in clinical practice. Despite oxygen being used routinely within this range in pre-term babies, it was defined as an IMP and therefore it required a greater burden of regulatory compliance. Once it is safe to do so babies are often moved from specialist units to 'step down' units to be nearer their parents. A child had to be withdrawn from this trial because, despite continuing to receive oxygen ventilation as part of routine care, the 'step-down' unit could not demonstrate the necessary compliance with regulations.

### **Contact details**

We would be happy to provide any further information or a representative to discuss the response further, as required. Please contact Layla Theiner, Cancer Research UK's Public Affairs Manager, at [layla.theiner@cancer.org.uk](mailto:layla.theiner@cancer.org.uk) or on 0044 (0)20 3469 8127.