Revision of the EU Clinical Trials Directive

A joint statement from non-commercial and commercial organisations

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. This statement outlines agreement on key issues relating to clinical trials although a more detailed proposal is needed.

What are clinical trials?

We invest in medical research with the goal of developing new drugs that help people live longer and healthier lives. Before these drugs (or 'medical products') can be provided to patients they must go through a series of controlled tests. We do this through clinical trials, which are conducted using healthy volunteers or patients, to establish whether a drug is safe and how well it works ('efficacy'). Clinical trials are a vital stage in developing and comparing drugs and identifying which medicines 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 and/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 1st 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 also 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.

What has been the impact of the CTD?

There have been concerns about the implementation and effectiveness of the Directive. 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 (see case studies 1-4).
2. The Directive has led to a greater administrative burden (with associated costs and delays) for clinical trials (see case studies 5 and 6). The assessment undertaken by the Impact on Clinical Research of European Legislation (ICREL)[1] 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 (case studies 5 and 6).

The European Commission announced on 10th 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:

Risk-based 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 (see case studies 3 and 4). 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 are in the Directive should be revised to ensure the scope of the Directive is clear and that studies are treated consistently across Member States.

[1] http://www.efgcp.be/downloads/icrel_docs/Final_report_ICREL.pdf

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 streatmline amendment and clinical study reporting. 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) and specifically support the option whereby the assessment is undertaken by 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 (e.g. the MHRA[2] 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. For example, the recent guidance on the current requirements for reporting suspected adverse serious adverse reactions (SUSARs) was welcomed[3]. Nevertheless, 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

Inconsistent interpretation of the Directive across Member States including definitions of key terms

Case study 1: Cancer Research UK is supporting EuroNet-PHL-C1, 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.

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[2] Medicines and Healthcare products Regulatory Agency (MHRA)

[3] http://eudravigilance.ema.europa.eu/human/docs/Detailed%20guidance%20CT3.pdf

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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.**

Case study 2: 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.

Case study 3: A **European Organisation for Research and Treatment of Cancer (EORTC)** phase III trial is currently being undertaken compares immediate versus deferred nephrectomy (a surgical procedure to remove the kidney) in patients with renal cell carcinoma. The principal objective of this study is to investigate whether deferring nephrectomy in routinely treated patients has an effect on disease control by optimising the sequence of surgery for this particular type of cancer. EORTC first assessed this study as being outside the scope of the Directive, the study question being clearly a surgery issue. However, the presence of background chemotherapy (the standard treatment prior to the patient joining the trial) has resulted in a divergent assessment by a UK network collaborating within this project. This assessment was initially supported by the regulatory authority in the UK (the MHRA). Follow-up discussions, led by EORTC, succeeded to convince all partners that the study was indeed a non-directive investigation. EORTC could proceed with the study successfully, though the activation of UK has suffered a major delay because of this discussion. Unfortunately, EORTC had several experiences of the same kind. **In some cases, studies were assessed as being under the scope of the directive in some countries, but not elsewhere.**

Case study 4: European Society for Paediatric Oncology (SIOP Europe) has found that many paediatric anti-cancer trials serve the improvement of treatment concepts and approaches using combinations of authorised medicines which are only available in off-label use for paediatric indications due to the lack of economic interest over the past decades. Paediatric investigator-driven cancer clinical trials are therefore hampered by the definition of an investigational medicinal product (IMP) as about 80% of anticancer drugs are in off-label use. Although first actions have been set to improve drug registration for paediatric indications (Introduction of PIP), regarding the current speed of progress, this will remain a problem in the future.

As paediatric cancer trials are mostly using drug combinations, most of these drugs are frequently considered as an IMP in the majority of Member States despite being in paediatric use for over twenty years. Some Member States consider all off-label drugs within a trial as IMPs whilst others restrict this definition to one drug only specifically under investigation within a randomised trial.

As a result of off-label use, the majority of multi-drug anti-cancer treatment protocols are regarded as clinical trials although standard treatment approaches (based on off-label use) are used. Relatively few paediatric cancer trials are performed within the framework of marketing authorisation whilst this amounts to 60 to 80% in adult indications. Differences in interpretation of the Directive by national regulatory authorities have had a disproportionate effect on trials in children, highlighted by differences in what is deemed an 'investigational medicinal product' when paediatric use of an old drug is outside its licensed indication. Insurance costs have increased 100-fold with no increase in actual risk between consecutive trials from the same study group[4]. For phase III trials, such interpretation of the need to declare multiple IMPs, even in the standard arm, has caused the paediatric oncology community to face significant increases in bureaucracy and obligations in terms of pharmacovigilance reporting, insurance and the provision of free drugs.

Increased burden due to a 'one size fits all' approach

Case study 5: 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 aimed 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 by the National Competent Authority as an IMP and therefore required a greater burden of regulatory compliance. The negative impact of the Directive was further demonstrated when a child had to be withdrawn from this trial when, despite continuing to receive oxygen ventilation as part of routine care, the 'unit to which they were transferred to be closer to their parents could not demonstrate the necessary compliance with regulations.

Case study 6: 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 CTD does not do enough to encourage regulatory authorities to take a risk-based approach, preventing similar cases in the future.**

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 or on 0044 (0)20 3469 8127.

[4] Pritchard-Jones K, SIOP Europe. Clinical trials for children with cancer in Europe - still a long way from harmonisation: a report from SIOP Europe. Eur J Cancer. 2008 Oct; 44(15):2106