

consultation

NOVEMBER 2009

NO. 3

Making clinical research less of a trial

EU consultation on the functioning of the Clinical Trials Directive

Key questions for NHS organisations

The consultation reviews the existing regulatory framework.

Key questions include:

- How could procedures for multinational trials be effectively streamlined?
- What changes could improve processes relating to ethics committees' assessments?
- How could inconsistencies in the way the existing Directive is applied in different EU countries be overcome?
- Should a more risk-based approach to clinical trials be introduced, and how could a system for differentiating risk operate?
- How could the participation of non-commercial organisations as sponsors of clinical trials be promoted?

The European Commission has launched a public consultation seeking views on how to improve the functioning of the Clinical Trials Directive. This *Consultation* outlines the key issues raised and seeks views from NHS organisations.

Background

Clinical trials are studies in humans aimed at testing the safety and efficacy of medicines. They are an essential part of the development of new medicines, and also have a role in the improvement of medical care more generally, for example, through trials comparing treatments or aiming to improve the use of medicines already on the market.

Many clinical trials involve multiple sites, including sites in several different countries, but, historically, different European countries have had different approaches to regulating clinical trials. The Clinical Trials Directive (Directive 2001/20/EC)

aimed to address this by simplifying and harmonising the administrative requirements for clinical trials, while ensuring:

- the protection of the health and safety of clinical trial participants
- the ethical soundness of the clinical trial
- the reliability and robustness of data generated in clinical trials.

The Directive was implemented in the UK in 2004.¹ It is widely accepted that the Directive has significantly improved the safety and ethical soundness of clinical trials in the EU,

1. Regulations 2004 (SI 2004/1031) and Amendment Regulations 2006 (SI 2006/1928).

'The consultation paper discusses in detail how the Directive is working, and considers various options for remedying shortcomings and unintended consequences'

in addition to improving cooperation between regulatory authorities in the EU countries.

However, a number of issues have also emerged which have contributed to making the EU a much less attractive location to carry out clinical trials. This has, in turn, restricted innovation and reduced the competitiveness of clinical research in the EU with knock-on effects for patients' access to new medicines and treatments.

The EU consultation

The consultation paper discusses in detail how the Directive is working, and considers various options for remedying shortcomings and unintended consequences that have become apparent since the implementation of the Directive. Through the consultation, the European Commission is seeking evidence of the strengths and weaknesses of the current legal framework, as well as views on the issues highlighted and ideas on how to address them.

Given the UK Government's commitment to research as an essential component of a high-quality healthcare system, and recent objectives to foster research in the NHS and to improve the UK environment for clinical trials, it is crucial that NHS organisations contribute their views.

Key issues

A number of areas have been identified where improvements could be made to make the EU a more attractive environment to carry out clinical trials. These include:

1. Multiple and divergent assessments of clinical trials

In order to carry out a clinical trial, the people wishing to run the trial (the 'sponsor') must first obtain a clinical trial authorisation (CTA) from the body responsible for regulating clinical trials in the country where the trial is planned (the National Competent Authority or 'NCA'). For multinational trials, a separate CTA is required for each country involved in the trial.

The Directive aimed to ensure that the regulatory requirements for authorisation of a clinical trial were the same throughout Europe by setting common rules for the authorisation regime by NCAs. However, experience shows that different countries' NCAs apply the rules differently, for example, often having different requirements for the content of CTA applications.

Although it is rare for NCAs to ultimately reach different conclusions about the award of the CTA, it is not unusual for different NCAs to make different requests for amendments to the research proposed. In practice, this means that the sponsors of multinational

The value of research and research governance in the UK

- Research is an essential component of a high-quality healthcare system, not an optional extra.
- Clinical trials in the UK have made a large contribution to improved care and there continues to be enormous research potential in the NHS with academic and commercial partners.
- The UK is engaged in a programme to develop better ways to foster research in the NHS as part of the Office for Life Sciences Blueprint implementation.
- The Department of Health's strategy Best Research for Best Health has made a start in the English NHS in tackling research bureaucracy.
- We have a shared interest in achieving high standards of research governance across the EU, but current procedures should be better coordinated and proportional to risk. Applying the same approach to trials with varying risk levels is a barrier to research. Often the effort of the bureaucracy outweighs the drive to carry out such studies. It is concerning that research opportunities are being lost in this way.
- The NHS needs to make the case for a risk-based system of research governance. Achieving this will encourage more research activity in the NHS and offer greater time and cost-effectiveness in discharging research governance.
- The NHS must challenge itself to suggest ways in which an amended EU Clinical Trials Directive can be designed to be fit-for-purpose to maintain patient safety and to promote high-quality research activity.

trials have to prepare a different CTA application for each participating country.

Furthermore, each clinical trial proposal is subject to an assessment by the ethics committee (EC) of the country concerned, in addition to that of the NCA. As different countries define the roles of the NCA and EC differently, it is difficult for NCAs to cooperate in assessment procedures. The views and requirements of ECs may also differ to an even greater extent between different countries.

Taken together, these factors have led to a major increase in the amount of work required and time taken to put together a multinational trial, as well as increased costs, to the extent that such trials have become prohibitively expensive for many small and medium enterprises, non-commercial sponsors and third-country sponsors.

Options to address these issues

NCAs have already begun to cooperate in the assessment of multinational clinical trial proposals, through a process called the Voluntary Harmonised Procedure (VHP). The first option proposed is further reliance on this voluntary approach. However, capacity is limited so even if all countries agreed, it would not be possible to assess all multinational trials through VHP. Furthermore, VHP still involves long delays in starting clinical trials.

The consultation document, therefore, also looks at options for streamlining the authorisation process, in particular, considering how a single CTA for multinational clinical trials could be realised. Two options are set out.

'Different countries have interpreted the Directive differently and have taken different approaches to implementation'

The first option would be a type of 'mutual recognition procedure', whereby one NCA – in the 'reference member state' – would carry out the assessment of the application on behalf of all the countries involved. Other NCAs would be consulted and could input, but ultimately the reference member state's assessment would be applicable across all countries concerned.

The second option would be to go for full harmonisation, with one body responsible for performing assessments and awarding CTAs valid across the whole EU. It is suggested that this body would draw on the scientific expertise of the European Medicines Agency (EMA), and work in cooperation with the European Commission and the EU countries.

The consultation document also considers the scope of such 'streamlined' procedures, noting that they could potentially be applied to all clinical trials carried out in the EU, or in a more limited way, such as:

- only to multinational trials
- only to trials investigating medicinal products for which a marketing authorisation issued by EMA is mandatory (for example, cancer drugs).

Would you support streamlining of clinical trial assessment procedures, as proposed? If so, which option would you prefer: increased use of VHP, the 'mutual recognition' approach or a fully harmonised model?

Although it is clear that assessment of ethical issues must remain a responsibility of the member states, the consultation paper also looks at whether any changes could be made to improve processes in relation to ECs' assessments.

In line with this, greater cooperation between ECs through the strengthening of existing networks is suggested. However, it is noted that every country's national ethics committee would retain the right to 'opt out' if they did not support the final result of an assessment, so no country could ever be 'out-voted' with regard to ethical issues.

The paper also proposes the clarification of the respective roles of NCAs and ECs, to make cooperation between bodies in different countries easier. In order to reduce the need for sponsors to submit information to multiple separate bodies, another idea proposed is that authorisation requests could be submitted to a 'one-stop shop'.

Would you support the options proposed in relation to ethics committees? Do you have any other suggestions about how processes in relation to ethics committees' assessments could be improved?

2. Inconsistent implementation of the Directive

Although the Directive aimed to harmonise requirements relating to clinical trials across Europe, this has only been achieved to a limited extent, as different countries have interpreted the Directive differently and have taken different approaches to implementation. The consultation paper identifies three particularly problematic areas.

Substantial amendments: the Directive's aim was to reduce the number of amendments to a clinical trial protocol which need regulatory agreement. The intention was to concentrate only on amendments that are 'substantial', for example, having implications in terms of participants' safety. However, different countries have different interpretations of what constitutes a substantial amendment. In practice, this leads to sponsors over-classifying amendments as substantial, as they lean towards over-reporting rather than risk non-compliance in some countries.

Adverse incident reporting:

under the Directive, all reports of suspected unexpected serious adverse reactions (SUSARs) related to a substance under investigation have to be reported to the NCAs and ECs of countries where any trial looking at that substance is running (even where separate trials may be looking at the substance in completely different settings). This has led to an overload of work for ECs, who are required to consider and act on all SUSARs.

Furthermore, each country is responsible for ensuring that SUSARs are reported to the Community database. However, different countries have developed different regimes, leading to multiple reporting and unreliable data on the Community database, in particular in relation to multinational trials.

While, overall, there has also been a six-fold increase in the average number of SUSARs reported since the implementation of the Directive, numbers vary disproportionately between some countries. The reasons behind these developments are not

clear, but the variation in regimes and multiple over-reporting may be contributing factors.

Scope: the Directive does not apply to 'non-interventional' trials – that is, trials of medicines that are already on the market, which observe 'normal' usage (and, therefore, are also referred to as 'observational' trials). The intention is that non-interventional trials should, in the future, be regulated as part of the EU framework for pharmacovigilance (the monitoring of medicines' safety), and proposals to this effect are currently going through the legislative process.

The rationale for the difference in approaches is that non-interventional trials are usually lower risk than interventional trials and, as they concentrate on activities which form part of normal clinical practice, they are in any case covered by the general medical surveillance of the patient.

However, different countries interpret the borderline between non-interventional trials and interventional trials, and therefore, when the Directive applies, differently. There is particular variation as regards trials which look at normal clinical practice, but with some extra monitoring, which some countries regard as non-interventional, while others consider that the Directive applies.

Options to address these issues

The consultation document identifies inconsistencies in the application of the Directive as the common cause for all these issues and therefore, looks at mechanisms to amend the legislative framework to address this.

'The consultation paper suggests that reviewing existing implementation guidelines could help ease many of the problems described'

The first option proposed would be to amend the Directive with a view to, amongst other things, clarifying:

- the rules on reporting of SUSARs
- the requirements for follow-up of SUSARs by NCAs and ECs
- the regime relating to substantial amendments.

However, a further-reaching option is also proposed, whereby the current Directive would be repealed and replaced by a Community regulation. Unlike directives, which have to be 'transposed' into national laws, regulations are directly applicable and therefore there is much less scope for differences in interpretation and implementation.

Do you think the problems identified are accurately described? Would you highlight any other issues arising from differences in implementation? Do you think the options proposed would solve these problems, or would you suggest alternative solutions?

3. Framework not always adapted to practical requirements

The consultation paper acknowledges that, in some areas, the Directive is inflexible, meaning that regulatory requirements cannot be appropriately adapted to different situations. Two such areas are identified.

Requirements not proportionate to risk: the level of risk to participants in a clinical trial depends on a range

'The right balance needs to be struck between protecting participants, ensuring the reliability of data, and facilitating the development of new medicines'

of factors such as the patient population involved and the level of knowledge and experience of the medicine being investigated. The Directive covers a very wide range of trials, from 'first-in-human' trials of new substances to trials aiming to improve treatments with medicines already on the market. Broadly the same requirements apply to all trials, for example, with regards to safety reporting and insurance requirements, with little or no flexibility for variation depending on the level of risk involved.

Requirement for a single sponsor: the Directive is based on the principle that there should be a single sponsor per clinical trial. This, however, creates problems in practice for multinational trials, as it is difficult for a sponsor, particularly those from academic and non-commercial sectors, to take responsibility for trials in other countries. The increased costs associated with doing this acts as a powerful disincentive to academic- and non-commercial-led clinical trials. It can also be difficult for an NCA, where necessary, to take action against a sponsor based in another country.

Options to address these issues

The consultation paper suggests that reviewing existing implementation guidelines, such as the rules for safety reporting, could help ease many of the problems described. However, it notes that only the more far-reaching approach of a

revision of the Directive itself could address issues such as the requirement for a single sponsor and insurance issues.

The paper also suggests the further, more radical, option of excluding clinical trials carried out by 'academic' sponsors altogether from the Directive, with each country setting its own rules for such trials. However, this would not facilitate multinational academic-sponsored trials, and would prevent the results of such trials from being used to support a marketing authorisation application.

Do you think the problems identified are accurately described? Would you highlight any other areas where the Directive would benefit from greater flexibility? Do you think the options proposed would solve these problems, or would you suggest alternative solutions?

4. Special types of clinical trials

The paper notes that some types of clinical trial have specific characteristics which make them potentially more difficult to carry out under the current framework. For example, there are concerns that requirements for paediatric clinical trials may be unnecessarily burdensome. Another example is clinical trials in emergency situations, which the requirement for informed consent may hinder. Although many

countries have taken steps to ensure such trials can take place, this has led to divergent views on what constitutes good clinical practice in this area.

The consultation paper suggests that a review of the Directive could consider possible changes to facilitate and promote special types of clinical trials, for example, the introduction of a specific regime for clinical trials in emergency situations.

What options could be considered with a view to promoting special types of clinical trials, such as paediatric clinical trials? Would it be useful to have a specific regime at EU level for emergency clinical trials?

5. Ensuring compliance with good clinical practices in third countries

The Directive requires all clinical trials carried out in the EU to comply with Good Clinical Practice (GCP) principles, but there is concern that, despite broad international agreement on what constitutes GCP, trials carried out in third countries may not always meet such rigorous standards.

Options to address the issue

The paper sets out a number of possible actions aimed at ensuring GCP principles are enforced for all clinical trials, no matter where they are carried out, including:

Many of the issues covered in the consultation will be of interest to NHS organisations involved in medical research and innovation in healthcare. The deadline for consultation responses is 8 January 2010. The NHS European Office will be coordinating a response on behalf of the NHS and would welcome contributions to this by **18 December 2009**. Further contributions would be welcome beyond this date, as the review is likely to be a lengthy process. However, the focus of discussion may change. Please email your views to jenny-lee.spencer@nhsconfed.org

- relying on European-based sponsors to ensure that clinical trials carried out in third countries are performed in accordance with international standards (effectively the status quo)
- supporting third countries where regulation of clinical trials is currently weak, for example, through partnership projects
- strengthening of international cooperation in GCP inspection activities and mutual recognition of GCP rules
- giving EMEA a mandate to assess third country trials if requested to do so by an international body such as the World Health Organization (WHO)
- requiring sponsors applying for CTAs in the EU to make information available about all the clinical

trials they carry out available in a public register

- greater scrutiny by European regulators of clinical trial results submitted to them, for example, as part of CTA or marketing authorisation applications, and by the European Commission of clinical trials receiving financial support from EU funding programmes.

Would you support any of the options proposed, or would you suggest any alternative approaches to ensuring GCP is enforced in third countries?

Summary

The regulation of clinical trials is an important but complex area, where the right balance needs to be struck

between protecting participants, ensuring the reliability of data and facilitating the development of new medicines that benefit patients and bring economic benefits to wider society.

There are clearly a number of issues which need to be addressed within the current framework, but finding solutions may not be straightforward, and revising legislation can be a lengthy process. Nevertheless, it is crucial that NHS organisations take this opportunity to make their views known and to feed in evidence supporting the need for change. The European Commission's consultation process offers a real opportunity to influence the future direction of the European regulatory framework and in the longer term, to improve the UK environment for carrying out clinical trials.

The NHS European Office

The NHS European Office has been established to represent NHS organisations in England to EU decision-makers. The office is funded by the Strategic Health Authorities and is part of the NHS Confederation.

EU policy and legislation have an increasing impact on the NHS as a provider and commissioner of services, as a business and as a major employer in the EU.

Our work includes:

- monitoring EU developments which have an impact on the NHS
- informing NHS organisations of EU affairs
- promoting the priorities and interests of the NHS to European institutions
- advising NHS organisations of EU funding opportunities.

Further copies or alternative formats can be requested from:

Tel 0870 444 5841 Email publications@nhsconfed.org
or visit www.nhsconfed.org/publications

© The NHS Confederation 2009. The use of this publication is covered by the conditions of Creative Commons Attribution-Non-Commercial-No Derivative Works License:
www.creativecommons.org/licenses/by-nc-nd/2.0/uk

You may copy or distribute this work, but you must give the author credit, you may not use it for commercial purposes, and you may not alter, transform or build upon this work.

Registered Charity no: 1090329

EUR00601

NHS European Office

Rue Marie Thérèse, 21, B-1000 Brussels

Tel 0032 (0)2 227 6440 Fax 0032 (0)2 227 6441

Email european.office@nhsconfed.org

www.nhsconfed.org/europe

