the voice of the NHS in Europe

NHS European Office

briefing

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Revising the Clinical Trials Directive

How proposed changes can help deliver clinical research in the NHS

Key points

- The proposed EU Regulation on clinical trials represents a substantial change from the current regulatory framework.
- The proposed changes are timely in light of the increasing importance of clinical research for the NHS.
- Many of the changes proposed are welcome and in line with amendments pressed for by the NHS European Office.
- We are seeking views on the proposals from NHS organisations in order to shape our response and to influence the EU decision-making process.

The EU Clinical Trials Directive, which was implemented in the UK in 2004, has been highly criticised for contributing to a significant drop in the number of clinical trials conducted in the UK. The European Commission, having recognised the need to remedy the unintended consequences of this EU law, has published legal proposals to amend the existing EU Directive. This *Briefing* outlines the key changes proposed and what they mean for the NHS. The proposals will be subject to negotiations at EU level and the NHS European Office will continue to brief EU decision-makers on NHS views.

Background

In July 2012, the European Commission issued a proposal for an EU Regulation on clinical trials on medicinal products for human use. The Regulation, once agreed, will repeal the existing EU Directive on Clinical Trials (Directive 2001/20/EC). This is the first revision of the EU Clinical Trials Directive and responds to wide criticism of the current regulatory framework voiced by many stakeholders from across Europe.

Clinical trials are studies on 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 across several different countries, but historically different European countries

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have had diverse approaches to regulating clinical trials. The Clinical Trials Directive 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 trials' participants, the ethical soundness of the trials, as well as the reliability and robustness of data generated.

While the Directive has significantly improved the safety and ethical soundness of clinical trials in the EU, the harmonisation objective has only been achieved to a limited extent, as member states have interpreted the Directive differently and have taken varied approaches to implementation. This has contributed to a number of unintended consequences at EU level, including:

- the number of applications for clinical trials fell by 25 per cent from 2007 to 2011
- the cost and administrative requirements of conducting clinical trials have significantly increased
- for non-commercial sponsors, the administrative costs increased by 98 per cent
- the average delay for launching a clinical trial increased by 90 per cent to 152 days.

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.

Key changes

The new proposed Regulation follows a lengthy consultation process conducted by the European Commission, with which the NHS European Office engaged extensively, putting forward NHS views and proposals on how the EU law could be improved.

The new legislation proposed by the Commission takes the form of a Regulation, meaning that the EU law, once agreed, will apply directly in each member state of the EU, without the need to be transposed into national law, and thus ensuring that the rules for conducting clinical trials will be more consistent throughout the EU. The NHS European Office has been pressing for changes to the existing Directive for a number of years and is pleased to see that the proposal reflects a number of amendments we have called for on behalf of the NHS.

The key changes from an NHS perspective are presented below.

1. Simpler authorisation procedure

In order to carry out a clinical trial, the organisation responsible for the trial (the 'sponsor') must first obtain an authorisation. The Regulation proposes a new streamlined authorisation procedure based on the submission of a single application dossier and a swift assessment procedure. This aims to remedy the difficulties caused by the current Directive, which requires the submission of separate application dossiers for each of the countries involved in a trial, and which has thus resulted in delays in the launch of clinical trials and in a disproportionate administrative burden.

The sponsor will submit the application dossier via an EU portal to be established by the European Commission, which will act as the single entry point for the submission of data and information relating to the trial and which will facilitate communication between the relevant authorities in member states and the sponsor. The application dossier shall contain all the documentation and information relating to the trial, as listed in the Regulation. Member states are encouraged to accept information and documentation in a commonly understood language in the medical field to ensure that the assessment of the applications for trials to be conducted in different countries functions smoothly.

Which clinical research is governed by the proposed EU Regulation?

As for the existing EU Directive, the new Regulation governs research on 'investigational medicinal products', which means studies involving the development of new medicines, or the use of medicines not in accordance with the terms of their marketing authorisation, or the improvement of treatments with medicines already on the market. As such, the law does not apply to 'non-interventional trials' – that is, studies which observe the 'normal' usage of a medicine which is already authorised. Equally, studies aiming to ascertain the safety and efficacy of medical devices or of clinical procedures, but not involving medicinal products, are not regulated by this EU law.

All member states in which the sponsor intends to conduct the trial will be involved in the assessment. Nevertheless, the Regulation draws a clear distinction between aspects of the application where member states concerned shall cooperate in the assessment and those aspects where each member state shall conduct their assessment individually, given their intrinsically national, ethical or local nature.

The aspects of the application dossier where member states shall cooperate in the assessment include:

- the anticipated therapeutic and public health benefits of the trial and the risks and inconveniences for the participants
- compliance with the requirements concerning the manufacturing, importation and labelling of investigational medicinal products
- completeness and adequacy of the investigator's brochure.

For these aspects, a single member state will act as the 'reporting' member state and as such be responsible for leading and coordinating the assessment and for liaising with the sponsor. The reporting member state will have to take into account any considerations on the application which the other member states involved may have.

On the other hand, the aspects of the application dossier which should be assessed individually by each member state concerned include compliance with requirements for:

- informed consent and recruitment of participants in the trial
- suitability of researchers carrying out the study and of trial sites
- insurance for damage compensation
- collection and future use of biological samples of the participants in the trial.

Each member state will be free to determine which body or bodies will be involved in the assessment. In the event that different bodies are involved, their assessments should, however, result in one single decision to be notified to the sponsor.

'We welcome the proposed streamlined authorisation process, which we believe will contribute to reducing the administrative burden for sponsors and speed up the launch of multinational clinical trials.'

The proposed Regulation provides clear timelines for the different steps in the authorisation process and maintains the concept of tacit authorisation to ensure that timelines are adhered to. It also provides for a mechanism to extend the clinical trial to one or more additional member states, without requiring the re-assessment of the application dossier by all member states involved in the initial authorisation.

Furthermore, the Regulation clarifies when modifications to an already approved trial should be subject to a new authorisation procedure. More specifically, it says that these modifications should have a substantial impact on the safety or rights of the participants in the trial, or on the robustness of the data generated.

2. Lighter regime for 'low risk' clinical trials

Addressing heavy criticism that the existing Directive has placed broadly the same obligations and restrictions on clinical trials

Why clinical trials are important for the NHS

- Research is an essential component of a high-quality healthcare system.
- Increasingly NHS trusts are becoming involved in clinical research and recruit patients in clinical trials; last year 99 per cent of trusts in England had some patients involved in research studies.
- Involvement in clinical studies facilitates earlier adoption of innovation in participating trusts and helps improve their performance and their ability to recruit consultants.
- Clinical trials allow NHS trusts to develop new treatments and to improve the quality of the healthcare they provide.
- Patients enrolled in clinical trials can benefit earlier from innovative drugs and treatments to which they would not otherwise have access.
- Commercial clinical research provides trusts with a potential source of additional income.

irrespective of their level of risk, the new Regulation seeks to introduce a regulatory regime more proportionate to the risk to participants in the trial.

To this end, it waives or reduces certain obligations in the case of trials aiming to improve treatments with medicines already on the market, taking into consideration the level of knowledge and experience with the medicine being investigated and thus the lower risk associated with these trials.

In particular, the Regulation identifies a new category of clinical trials, called 'low interventional', which are subject to more proportionate rules around different aspects of the clinical trial process, including timelines for authorisation, monitoring, reporting, traceability and storage of investigational medicinal products, and insurance for damage compensation.

To be considered as 'low interventional', a clinical trial will have to fulfil all of the following conditions:

- the investigational medicinal products are authorised
- the investigational medicinal products are used in accordance with the terms of the marketing authorisation, or their use is a standard treatment in any of the member states concerned
- the additional diagnostic or monitoring procedures do not impose more than minimal additional risk or burden on the safety of the participants in the trial compared to normal clinical practice in any member state concerned.

We welcome this innovation in the EU proposals, which is in line with recent efforts domestically to develop a risk proportionate regulation in clinical trials. We will now consider how the EU proposal could be further improved in this area.

3. Co-sponsorship will be possible

Each clinical trial must have a 'sponsor', which is the organisation responsible for initiating and managing the clinical trial. While the existing Directive was based on the principle that there should be a single sponsor per clinical trial, the proposed Regulation explicitly introduces the concept of co-sponsorship. This is particularly important for the UK, which interpreted the original EU law as allowing trials to be sponsored by more than one organisation, meaning the sponsor's responsibilities may be shared between two or more organisations.

The co-sponsorship model is widely used by NHS trusts, which often lead clinical trials jointly with their partner universities. In light of this, we pushed hard for co-sponsorship to continue to be allowed and are very pleased to see this concept explicitly included in the draft Regulation.

The proposal allows the co-sponsors to either be all responsible for the entire clinical trial or to split the sponsor's responsibilities between themselves through a contractual agreement. In any event, the co-sponsors will have to nominate one from among them as the organisation responsible for acting as the contact point for information on the whole clinical trial, and for also ensuring compliance with the obligations related to the authorisation process.

'As the vast majority of EU member states requires a single sponsor per trial there was a real risk that the new EU Regulation could have explicitly banned any co-sponsorship arrangements in the future.'

4. Simpler safety reporting

Under the existing Directive, all reports of suspected unexpected serious adverse reactions (SUSARS) related to a substance under investigation have to be reported to the national competent authorities and ethics committees of the countries where any trial looking at that substance is running.

Furthermore, each country is responsible for ensuring that SUSARS are reported to the European database. These requirements, as well as other reporting obligations in the rules, have led to an overload of work both for researchers and for ethics committees and to the development of different reporting regimes in different countries.

To address these problems, the Regulation proposes more streamlined and simplified reporting procedures, as follows:

- the possibility to exclude reporting by the investigator to the sponsor of adverse events, if this is provided in the protocol
- direct reporting of SUSARS by the sponsor to the European database
- simplified submission of the annual safety report by the sponsor.

5. Compensation for damages

The Directive introduced the obligation to have in place insurance or indemnity to cover the liability of the investigator and the sponsor in each clinical trial. This obligation has substantially increased the costs and administrative burden of conducting clinical trials and has created difficulties specifically for NHS trusts sponsoring multinational clinical trials in terms of their ability to get insurance/ indemnity for clinical trials sites outside the UK.

To address this, the Regulation proposes that for those clinical trials which pose only negligible additional risk compared to treatment in normal clinical practice, no specific insurance or indemnity is required. The proposed Regulation also requires member states to set up a national indemnification mechanism working on a not-for-profit basis to help non-commercial sponsors comply with insurance/ compensation requirements for trials. This approach is a positive development for the NHS, but it may be difficult to maintain during the course of negotiations as we expect some member states to oppose it.

'These proposals represent an opportunity to enhance NHS involvement in multinational trials.'

6. Protection of participants and informed consent

The proposed Regulation does not change the substance of the existing rules in this area. Nevertheless, it introduces new rules for the specific situation where, because of the urgency of the situation, it is not possible to obtain free and informed consent from the participants in the trial or from their legal representatives.

For these clinical trials in emergency situations, in line with international guidance, the Regulation specifies that consent may be obtained after the start of the trial only when all the following conditions are met:

- due to the urgency of the situation, caused by a sudden life-threatening or other serious medical condition, it is impossible to obtain prior informed consent from the subject
- no legal representative is available
- the subject has not previously expressed objections known by the investigator
- the research relates directly to a medical condition which makes it impossible to obtain prior informed consent
- the clinical trial poses a minimal risk to, and imposes a minimal burden on, the subject.

7. Manufacturing and labelling of investigational medicinal products

The proposed Regulation brings together rules on the manufacturing, importing and labelling of medicinal products used in clinical trials which are currently contained in different EU Directives and guidelines.

It also provides clarification on the extent to which rules in this area apply to investigational medicinal products which have already received market authorisation and to auxiliary medicinal products (ie, medicines which are used in the context of the clinical trial but that are not investigational medicinal products).

Furthermore, the Regulation specifies that manufacturing authorisation is not required for the following processes, which would instead be subject to alternative national proportionate requirements:

- relabelling, repackaging or reconstitution prior to use or packaging, where these processes are carried out by authorised hospital pharmacists
- the manufacture or import of radiopharmaceuticals used as diagnostic investigational medicinal products where those processes are carried out in hospitals by pharmacists.

8. Requirement of a master file

The Regulation requires the sponsor and the investigator to keep a clinical trial master file, which shall allow verification of the conduct of the trial. The content of the master file shall be archived for at least five years after the end of the clinical trial. Access to the archived information shall be restricted to nominated individuals within the sponsor's organisation.

Next steps

The proposed Regulation will now pass through the EU legislative procedure, with agreement needed between the European Parliament and the Council of Ministers. The negotiations will last for several months during which the NHS European Office will continue to brief EU decision-makers on NHS views.

We welcome many of the changes proposed in the Regulation, and will seek to ensure that they are maintained during the EU decision-making process and that the agreed final text is fit for purpose in terms of maintaining patient safety and promoting high-quality research in the NHS.

Once agreed, the Regulation will repeal Directive 2001/20/EC. Nevertheless, in order to ensure smooth transition to the new regulatory regime, it is suggested that both sets of rules will apply in parallel for a period of three years after the date of entry into force of the Regulation.

We seek views on the proposed Regulation and its implications for conducting clinical research in the NHS and will establish an expert group to this end. If you would like to join this group, or contribute views, or discuss any aspect of the proposals, please contact **elisabetta.zanon@nhsconfed.org**

Further information

To view the text of the proposed Regulation or the NHS European Office's responses to the European Commission consultations on the revision of the Clinical Trials Directive, see: **www.nhsconfed.org/NationalAndInternational/NHSEuropeanOffice/influencingEUpolicy/clinical-trials/Pages/Clinical_trials_directive.aspx**

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 healthcare, 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.

To find out more about us, and how you can engage in our work to represent the NHS in Europe, visit **www.nhsconfed.org/europe** or contact **european.office@nhsconfed.org**

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