

Briefing

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The new EU Clinical Trials Regulation How NHS research and patients will benefit

Who should read this briefing?

- This briefing will be of interest for all involved in clinical research, including senior board members.
- Given the importance of the issue to the innovation agenda, it will also be of interest to academic health science centres and networks.

What this briefing is for

- This briefing outlines the key changes made by the new EU Regulation on clinical trials and what they mean for the NHS.

Key points

- Clinical trials are an essential part of the development of new medicines, and also have a role in the improvement of medical care more generally.
- The authorisation and the conduct of clinical trials are regulated by EU law, as trials are often conducted in multiple sites across a number of European countries.
- A new EU law will address shortcomings of the existing EU Clinical Trials Directive, which contributed to a significant decrease in the number of clinical trials conducted in the UK.
- The changes it will bring are timely in light of the increasing importance of clinical research in the NHS and the establishment of academic health science networks.
- The new law will in particular allow for the speeding up of the process for authorising new clinical trials and reduce the administrative burden associated with the conduct of these studies.
- The EU Regulation is expected to apply from 2016 to allow time for the EU portal and database to be up and running.

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Background

Clinical trials are studies conducted on humans aimed at testing the safety and efficacy of medicines. They are an essential part of the development of new medicines and 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. The process for the authorisation and conduct of clinical trials is regulated by EU law. This is because trials are often conducted in multiple sites across a number of European countries and, therefore, there is a need for harmonisation of the rules at EU level.

In summer 2012, the European Commission issued a proposal for an EU Regulation on clinical trials on medicinal products for human use, to replace the existing EU Directive on Clinical Trials (Directive 2001/20/EC). The revision of this Directive was pressing due to criticism voiced against it by many of those involved in clinical research across Europe.

Since its application in 2004, the EU Clinical Trials Directive has contributed to a dramatic drop in the number of clinical trials with EU, and UK, involvement. The European Commission's figures show that from 2007 to 2011:

- the number of applications to carry out clinical trials in the EU fell by 25 per cent
- costs increased significantly
- delays for launching a clinical trial rose by 90 per cent.

This has 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 proposal for a new EU law on clinical trials went through a lengthy EU decision-making process. The Regulation entered into force on 16 June 2014. The EU Regulation is, however, expected to be applied only from 2016 to allow sufficient time for the development and testing of the EU portal and database which will support its implementation.

Key changes

The new EU Regulation (536/2014) addresses many of the shortcomings which resulted from the Clinical Trials Directive. In particular, it will:

- streamline the procedures to assess and authorise new clinical studies, removing duplications and reducing delays for launching clinical trials
- introduce a lighter regulatory regime for trials conducted with medicines which are already authorised and which pose only minimal risk compared to normal clinical practice
- simplify reporting requirements, sparing researchers from submitting largely identical information on the conduct of the study separately to various bodies
- recognise that a trial can be led by more than one organisation, by formally introducing the concept of 'co-sponsorship'; this is of great importance for many NHS trusts which have co-sponsorship arrangements in place with their academic partners.

Importantly, the new EU law takes the form of a Regulation, meaning that it will apply directly in each member state of the EU without the need to be transposed into national law, and thereby will ensure the rules are consistent throughout the EU.

The NHS European Office engaged extensively with the process of revision of the existing Clinical Trials Directive, pressing hard for a number of important changes to be made. We welcome the new Regulation, which reflects many of the amendments we called for on behalf of the NHS.

“The NHS European Office engaged extensively with the process of revision of the existing Directive.”

A simpler authorisation procedure

The Regulation introduces a new and streamlined procedure to authorise the launch of new clinical trials, based on the submission of a single application and swift assessment. This is to remedy the difficulties caused by the current Directive, which requires submission of separate applications for each of the countries involved in a trial and has thus resulted in delays in the launch of clinical trials and a disproportionate administrative burden.

The EU portal

Under the new Regulation, the 'sponsor' – the organisation responsible for initiating and managing the clinical trial – will submit the application via an EU online portal. This will act as the single entry point for the submission of information and data relating to the trial, and will facilitate communication between the relevant authorities in member states and the sponsor.

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

The 'reporting' member state

For the aspects of the application where member states will cooperate in the assessment, namely those concerning the type of clinical trial, the risk-benefit analysis and compliance with technical requirements, a single member state will act as the 'reporting' member state and be responsible for leading and coordinating the assessment and liaising with the sponsor. The reporting member state will have to take into account considerations on the application which the other member states involved may have.

Individual assessments

For the aspects of the application which should be assessed individually by each member state concerned, those that have an intrinsically national nature, such as compliance with the requirements for informed consent and compensation of participants in the event of harm, 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.

Process timelines

The Regulation provides specific timelines for the different steps in the authorisation process and confirms 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 reassessment of the application by all member states involved in the initial authorisation. It also clarifies when modifications to an already approved trial should be subject to a new authorisation procedure.

A lighter regime for low-risk clinical trials

Addressing criticism that the existing Directive has placed broadly the same obligations on clinical trials irrespective of their level of risk, the new Regulation identifies a new category of clinical trials – low interventional. Low interventional clinical trials are subject to more proportionate rules with regards to some aspects of the clinical trial process, including monitoring, reporting, traceability and storage of investigational medicinal products.

To be considered as low interventional, a clinical trial will have to be conducted with medicines which are already authorised and used in accordance with the terms of the marketing authorisation or, in case of use off label, their use should be evidence based and supported by published scientific evidence on safety and efficacy. Furthermore, the additional diagnostic or monitoring procedures should not pose more than minimal additional risk or burden to the safety of the participants compared to normal clinical practice.

While the NHS European Office welcomes this innovation, as many of the trials sponsored by NHS organisations investigate treatments with medicines which are already authorised, we believe that more could have been done by EU decision-makers to systematically reflect a risk proportionate approach in the different parts of the regulatory framework.

Streamlined safety reporting

Under the existing Directive, researchers have to separately submit largely identical information on the safety of the clinical trial to various bodies and member states. The new Regulation removes duplications by introducing streamlined reporting procedures based on a centralised EU database for safety reporting.

In response to specific concerns raised by NHS organisations, the Regulation provides for the possibility of submitting a single annual safety report on all the investigational medicinal products used in one trial instead of individual reports for each of the medicinal products. This is of particular importance for NHS-sponsored trials, which often compare medical treatments based on the combined use of different medicinal products.

Another important change is the possibility of streamlining the requirements for the recording and reporting of adverse events by the investigator to the sponsor.

Formal recognition of co-sponsorship

Each clinical trial must have a sponsor. 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 NHS, as the original EU law was interpreted domestically 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 organisations, which often lead clinical trials jointly with their partner universities. In light of this, the NHS European Office pushed hard for the concept of co-sponsorship to be explicitly recognised in the Regulation. As the vast majority of EU member states require a single sponsor per trial, there was a serious risk that the new EU Regulation could have banned any co-sponsorship arrangements in the future.

Greater transparency in clinical trials

Reporting milestone events

While the current regime requires limited notifications by sponsors of events related to the lifecycle of a clinical trial, the new Regulation puts in place a more systematic notification system whereby all milestone events must be reported. In particular, the sponsor must notify, via the EU portal, the following events within 15 days:

- the start of the trial
- the first visit of the first subject
- the end of subject recruitment
- any temporary halt
- the end or early termination of the trial.

Results on EU database

Importantly, the Regulation introduces requirements for sponsors to submit a publicly available summary of the results of the trial within one year of its end. The detailed content of this report is specified in an annex to the Regulation and the submission of this information is required irrespective of the outcome of the clinical trial. Furthermore, for clinical trials which have led to a request for marketing authorisation, a full clinical study report will have to be submitted for publication in the EU database.

The information above, as well as a simplified summary of the results for a larger audience, will be publicly accessible through the EU database with the exception of personal data and confidential commercial information. This will allow both researchers and patients to be aware of past trials and their outcomes.

“The new Regulation removes duplications by introducing streamlined reporting procedures.”

Protection of participants

Informed consent

The Regulation introduces more detailed rules on informed consent by subjects participating in clinical trials. It clarifies that in the case of 'cluster trials', where the methodology requires that groups of subjects rather than individual subjects are allocated to receive different investigational medicinal products, simplified means for obtaining informed consent can be used.

The Regulation clarifies that it is possible for participants to give broad consent so that data generated from the clinical trial in which they participate can be used for future scientific research. It also introduces new rules for when trials are conducted in emergency situations and therefore it is not possible to obtain prior informed consent from the participants or their legal representatives. Specific provisions are made for pregnant or breastfeeding women taking part in clinical trials.

Compensation

The Regulation specifies that member states must ensure systems are in place for compensation for any harm suffered by subjects during a clinical trial, and that sponsors and investigators must make use of these systems.

Next steps

The EU Regulation is expected to be applied from 2016, to allow sufficient time for the development and testing of the EU database and portal which will support its implementation.

During this time, UK legislation on certain elements of the EU Regulation will be drafted and agreed upon. Amongst other things, this will cover issues around ethics committees' approval, who will be allowed to conduct the interview with participants in the trial to get their consent, and rules around enforcement and compensation in case of harm.

The European Commission will be required to produce secondary implementing legislation and guidelines to provide more detail and clarity on different aspects of the Regulation.

The NHS European Office will monitor and engage with the implementation process to ensure NHS views continue to be fed into the discussions.

If you would like more information on the issues covered in this briefing, please contact elisabetta.zanon@nhsconfed.org or visit www.nhsconfed.org/europe

Why clinical trials are important for the NHS

- Research is an essential component of a high-quality healthcare system.
- Involvement in clinical studies facilitates earlier adoption of innovation and helps improve trusts' performance and ability to recruit consultants.
- Clinical trials allow NHS trusts to develop new treatments and 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.

Which clinical research is governed by this EU Regulation?

As with the existing EU Directive, the new Regulation governs research on 'investigational medicinal products' – 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.

It does not apply to 'non-interventional trials' – studies which observe the 'normal' usage of a medicine 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.

View from the NHS: University Hospitals of Leicester NHS Trust

University Hospitals of Leicester NHS Trust (UHL) is enthusiastic about the changes being brought about through the revised EU Regulation. Research is part of core business at UHL and it is essential to provide patients with as many treatment options as possible.

Historically, researchers have been reluctant to become engaged with research involving medicinal products because of the seemingly overbearing bureaucracy which has stifled the speed of progress. We expect that the new legislation will encourage more researchers to become involved in and design more varied studies, which will ultimately benefit more patients in many more disease areas.

It will also bring with it further collaborations with our existing partners, and encourage new and exciting opportunities for greater partnerships to evolve.

Within the document, on an operational level, areas of particular note are: the application processes, the emphasis on consent, centralised safety reporting and the new initiatives for transparency. The application processes will make it easier for Europe-wide, multi-centre studies to become a

reality for non-commercial sponsor organisations as well as for commercial partners. This is likely to produce an opening for new and varied avenues for clinical data comparisons.

What we are particularly interested in is ensuring that individuals in emergency situations also have access to research. We welcome the pragmatic approaches adopted in the changes as well as the opportunity for broader consent.

It is often difficult to access the latest information about a particular product in a disease area; the emphasis on transparency and the speed required for publication is welcomed.

Ultimately, we are encouraged by this document and the message that it conveys about speeding up processes to allow greater and more varied access to treatment and different care pathways for patients. The research arena is changing dramatically over the next couple of years – it is an exciting time!

*Carolyn Maloney, Head of Research Operations,
University Hospitals of Leicester NHS Trust*

The NHS European Office

The impact of the EU agenda on the NHS is constantly increasing, bringing with it both challenges and opportunities. The NHS European Office is the conduit for the NHS to engage with the EU agenda. Hosted by the NHS Confederation, we are the representative body for the range of NHS organisations in England on EU affairs. Our work includes:

- monitoring and influencing EU policy and legislation in the interest of the NHS
- facilitating access to EU funds for NHS bodies and their partner organisations
- supporting pan-European collaborations and sharing successful EU practices.

For more information on EU affairs of importance to the NHS and to get in touch with the NHS European Office, visit www.nhsconfed.org/europe or email european.office@nhsconfed.org

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