Are you ready?

The impending introduction of EU Clinical Trials Regulation No 536/2014

Photography by Isy & Leigh Anderson

Companies and organisations conducting clinical trials in the EU are about to see the largest shake up of legislation for decades with the introduction of the EU-Clinical Trials regulation (EU-CTR).

Introduction

Whilst these changes will streamline and improve the legislative and regulatory framework for clinical trials across Europe, they also pose significant challenges for sponsors.

This article, in brief overview, reviews the latest timelines for the introduction of the EU-CTR and outlines the most significant changes that this new regulation will bring to the operation of clinical trials in Europe.

Implementation timeline

In July 2012 the European Commission published the draft EU Clinical Trial Regulation to repeal the Directive 2001/20/EC, which was subsequently approved in April 2014 and published in the Official Journal of the European Union on 27 May 2014.

The EU-CTR legally entered into force on 16 June 2014, but will only apply upon satisfactory completion of the development of EU portal and database by the European Medicines Agency (EMA).

Updated timelines for completion of the EU Portal and Database were provided at the EMA Management Board meeting in December 2015 (http://goo.gl/mvDMhZ). The Board predicts that the database and portal will now be available for independent audit by August 2017. Provided that the portal and database satisfactorily pass audit, the EU-CTR will come into full effect by October 2018 at the latest.

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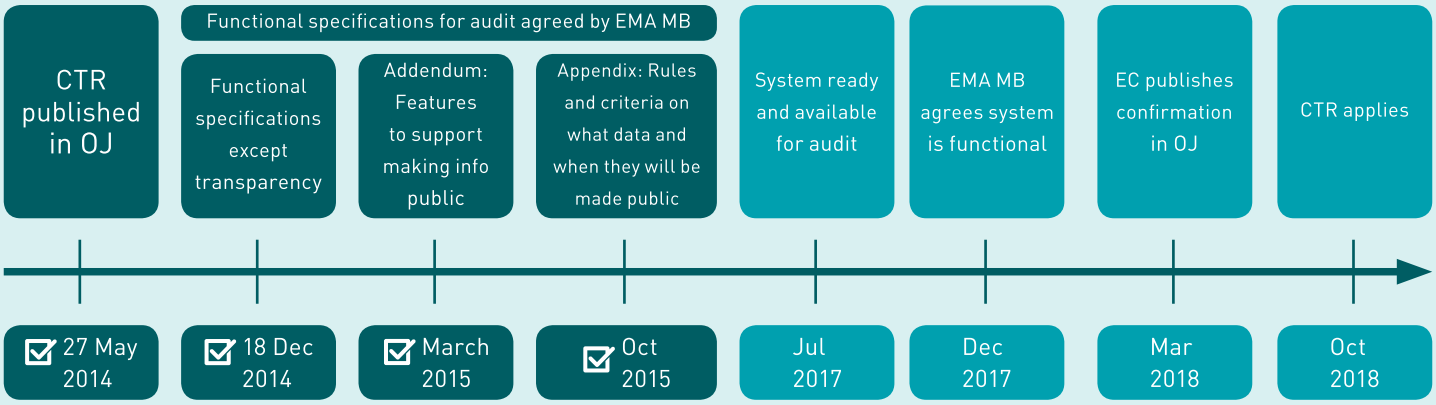
After reading this article, readers will be better equipped to work within the changing clinical trials landscape. Some of the key points covered are:

- How regulations relating to EU clinical trials are changing
- Why these changes are being made
- When the changes will come into effect
- Key milestones to know about

Figure 1: EMA key milestones and timelines for design and development of the EU portal and the EU database



Source: EMA 2016, CTR (OJ: Official Journal of the EU / EC: European Commission, MB: Management Board)

Why is Directive 2001/20/EC being replaced?

The EU Clinical Trials Directive 2001/20/EC (EUCTD) was approved in 2001 and implemented in May 2004. The EUCTD brought together an approximation of the laws, regulations and administrative provisions of member states relating to the conduct of clinical trials on medicinal products for human use and including the principles of Good Clinical Practice (GCP).

Despite positive intentions, EUCTD failed to achieve its objectives of simplifying and harmonising the regulatory environment for clinical trials across Europe. Instead, EUCTD interpretation varied widely between different member states which in turn led to high costs, a greatly increased regulatory and administrative burden for sponsors, and study delays especially for multicentre trials conducted across different member states. These EUCTD problems are believed to have contributed to a 25% decline in clinical trial activity across Europe since its introduction[1].

The introduction of the EU-CTR aims to restore the EU's competitiveness in clinical research by reducing administrative requirements and improving efficiency though streamlined workflows, such as the introduction of a single application process for all member states.

Why will the introduction of the CTR make a difference?

Whilst an EU directive is open to individual member state interpretation, a regulation is uniformly applicable in all member states. An EU regulation does not require the implementation of legislation at a national level and so removes the potential for variations in interpretation between member states and leads to a fully harmonised approach.

In practical terms this should lead to a reduction in costs and delays, along with a reduction in the administrative and regulatory burden commonly associated with conducting trials across multiple EU member states. This should make it easier for companies to conduct multicentre trials and ultimately lead to an increase in the number of studies conducted within the EU.

Replacing Directive 2001/20/EC with the CTR will lead to a fully harmonised approach across the EU.

What are the major changes in the EU-CTR?

The following points are not exhaustive but provide a very brief overview of the substantive changes contained in the EU Clinical Trials Regulation

A single application process

The introduction of the EU-CTR will provide for submission of a single application dossier for clinical trial authorisation across multiple EU member states. A new EU portal is under development to support single application and decision process by all member states where arms of trials will be conducted, leading to a streamlined application and approval process and reductions in administrative burdens.

Authorisation requirements for a Substantial Modification

To improve safety measures and transparency, a new term 'Substantial Modification' has been introduced which differs from the previous terminology of 'Substantial Amendment'. Substantial modifications to clinical trials will be required to undergo a similar (although shorter) authorisation process to the original application via the EU portal.

The definition of a 'substantial modification' may include addition of a new trial site, a change to a principal investigator, or a change to any aspect of a trial that has *'a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial'*.

Whilst these requirements may represent a new burden to the running of clinical trials, the process is streamlined through use of the EU portal with strict timelines applied to both sponsor and regulators.

Reporting of milestones and events by the sponsor on the EU portal

To facilitate effective supervision of trials by member states, there are additional requirements for sponsors to report key trial milestones within defined timescales, as well as requirements to report any temporary halts, restarts or early trial terminations.

There are also changes to the timelines and requirements for reporting of:

- Any breaches of protocols 'likely to affect to a significant degree, safety/rights of subjects and the reliability/robustness of the data'
- Unexpected events affecting the risk/benefit profile of a trial;
- Reporting of urgent safety measures

Applicability of ICH GCP guidelines

Whilst ICH GCP guidelines must be taken into account, if there are discrepancies between ICH GCP E6 and the CTR, the requirements of the Regulation will take precedence.

New classifications of research

On implementation of the EU-CTR, there will now be three categories of study: clinical trials, non-interventional studies and a new third category called low-interventional clinical trials.

A 'low-interventional clinical trial' is defined as a non-interventional study by design, but one that includes diagnostic or monitoring procedures that have a minimal impact or risk for patients. Less stringent rules will apply to low-intervention clinical trials e.g. in requirements for monitoring, IMP traceability and Trial Master File content. Additionally, member states will not require additional indemnity or insurances for these trials.

The introduction of this new category of trial has been designed to provide clarity for sponsors wishing to conduct non-interventional studies, and resolve conflicts created by the third arm of the definition of a non-interventional trial in the 2001 Directive.

This third definition of a non-interventional trial was worded as follows: *'A trial in which no additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data.'*

Under EUCTD, problems arose because this definition was open to widely differing interpretations by each of the 28 member states at the time. For example, in some countries a requirement to draw blood was interpreted as a reason to classify research as a clinical trial whereas in others the study was classified as non-interventional.

Sponsors must take particular care to classify studies correctly to gain approval.

Introduction of auxiliary medicinal products

A new definition of Auxiliary Medicinal Products (AMP) has been introduced. An AMP is defined as a product used within the clinical trial and described in the protocol, but is not an investigational medicinal product itself. Full Good Manufacturing Practice requirements will apply to AMPs, although some exemptions will apply.

Informed consent provisions

Substantive changes have been made to provisions for informed consent. These include both content of information and the processes used for gaining consent, but with simplified consent requirements for some cluster trials.

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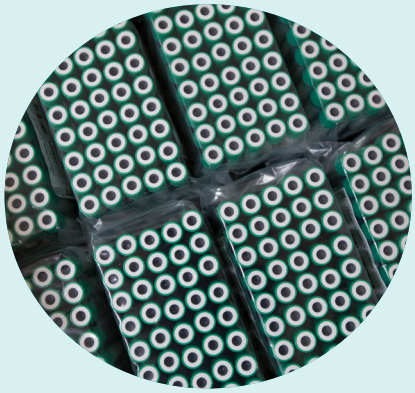
The Regulation also specifies measures to ensure the protection of vulnerable subjects, for example trials on pregnant and breastfeeding participants, and provides for the introduction of a Legally Designated Representative in relation to informed consent for minors and incapacitated adults.

Safety reporting requirement

The Regulation simplifies safety reporting requirements. Under Directive 2001/20/EC, suspected unexpected serious adverse reactions (SUSARs) and



Development Safety Update Reports must be individually submitted to the competent authorities and ethics committees of the different concerned member states. These will now be submitted through the Eudravigilance database of the European Medicines Agency (EMA), and will be directly forwarded to the member states.

All medication errors, pregnancies, misuse or abuse of investigational medicines are now subject to the same reporting obligations as adverse reactions.

Transparency

To reflect increasing demands from researchers and the public alike for improved transparency and disclosure of clinical trial results, the EU-CTR has put into place new provisions for the reporting and public disclosure of clinical trial results.

Sponsors must now submit a summary of clinical trial results to the EU database within a year of the end of the trial, or within 30 days of a marketing authorisation decision (whichever is the sooner) and include study summaries written in plain language for the layperson.

Trial master file and archiving

Both the sponsor and investigator trial master files must now be archived for a minimum of 25 years.

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Summary

The EU-CTR will introduce major changes to the administrative processes and procedures that govern the authorisation and conduct of clinical trials in the EU. The implementation of major changes like these inevitably adds some complexity during the transition phase. However, the changes will ultimately result in harmonisation across all EU trials, and support sponsors in achieving drug approvals across multiple EU regions through decreased complexity and greater efficiency.

Sources

Delivery time frame for the EU portal and EU database

http://goo.gl/qKwx4n

http://goo.gl/IhpXc4

Clinical trials - Regulation EU No 536/2014

http://goo.gl/htGHw6

References:

1. Markus Hartmann. Impact assessment of the European Clinical Trials Directive: a longitudinal, prospective, observational study analyzing patterns and trends in clinical drug trial applications submitted since 2001 to regulatory agencies in six EU countries. Trials. 2012; 13: 53.

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