The EU Clinical Trial Regulation –
A regulator’s perspective

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Keywords
Clinical Trial Directive (the Directive); Clinical Trial Regulation (CTR); European Medicines Agency (EMA); European Commission (COMM); Medicines and Healthcare products Regulatory Agency (MHRA); Member state (MS); Ethics Committee; EU portal and database; Transparency; Authorisation process; Delegated Act; Good clinical practice (GCP); Clinical trial application (CTA); Audit.

Abstract
The Clinical Trial Regulation (the Regulation) was approved and published in May 2014, ten years after the implementation of the Clinical Trial Directive (the Directive). There has been much criticism of the Directive which it is hoped the Regulation will put right, and make the EU a more attractive place to conduct clinical trials.

Although the Regulation will apply directly in all EU member states (MS) without the need for transposing into national legislation, there is much to do, both at an EU and MS level, to prepare for it. A key aspect of the implementation of the Regulation is the work being done on an EU portal and database. Confirmation by independent audit of this system’s full functionality is the key determinant for when the Regulation can apply.

In parallel with this work, many MS will also need to develop IT systems to support the Regulation implementation. There is also a need for development of national legislation to support the application of the Regulation in MS as well as a package of communication and training activities to ensure that research communities across the EU are prepared.

Background
The introduction of the Clinical Trial Directive 2001/20/EC (the Directive) in May 2004 significantly improved and harmonised the regulation of clinical trials across the EU compared with what previously existed, but it remained a much criticised piece of legislation and is perceived largely to have failed to live up to expectations. It provided a legal basis for good clinical practice (GCP) and ethical review for all trials and described a standardised approach for the application and approval of clinical trial authorisations (CTAs) as well as the conduct of the trial. Unfortunately inconsistent interpretation and implementation by the MS often resulted in increased complexity and uncertainty for sponsors and created an additional administrative burden as well as increasing costs and the potential to delay trial starts.

In July 2012 the European Commission published a draft legislative proposal for a Regulation on clinical trials with the objective of addressing these issues and making the EU a more attractive place to conduct clinical trials by:

• Providing a modern, consistent regulatory framework for submission, assessment and regulatory follow-up of trials
• Taking account of appropriate adaptations for risk and other practical considerations
• Addressing the global dimension of clinical trials when ensuring compliance with GCP.

This original proposal from the Commission included some major changes in the way clinical trials would be regulated in the EU and provided a sound initial basis for debate and negotiation by the European Parliament and the Council of Ministers, the EU co-legislators.

The EU Clinical Trial Regulation 536/2014 was negotiated and agreed in the relatively short period of only 18 months for such a complex and technical piece of legislation. This was in no small part down to the leadership of the EU Parliament rapporteur, Glenis Willmott, and to the Cypriot, Irish and Lithuanian Council Working Party Presidency teams. It was formally approved in April 2014 and published by the Commission in the Official Journal of the European Union on 27 May 2014 and entered into force 20 days later on the 16 June 2014. It will apply no earlier than 28 May 2016, but will depend on the development of the EU portal and database. Key differences between the Clinical Trial Regulation and Directive are:

• Regulation – A significant change by the Commission was that its proposal was for a Regulation and not a Directive and therefore would be directly applicable in all MS.
• Scope – Remains identical to the current Directive and applies only to interventional trials of medicines.
• Definitions – Most remain substantially the same as in the Directive except for:
  • Clarification of “clinical trial” and “non-interventional study”
  • Introduction of “low-intervention” clinical trial to allow simplification of the rules for lower-risk trials
  • “Substantial Amendment” changed to “Substantial Modification”
  • Introduction of “legally designated representative” in relation to informed consent for minors and incapacitated adults, to avoid confusion with legal representative of the sponsor
  • Introduction of “Auxiliary Medicinal Product” to replace the term “non-IMP” used in guidance.
• Authorisation process – The single biggest change is the introduction of an EU portal and database to allow a single point of entry for a single submission by sponsors to all MS concerned in their trial. This encompasses regulatory, ethics and public registration requirements in one package, regardless of the number of MS involved. For multinational trials, MS are required to work together in a coordinated assessment with one taking the lead.
Within MS, the national competent authorities (NCAs) will have to work together with ethics committees to form a single MS decision for each trial. Timelines have been extended slightly to allow this interaction to be reliably possible in all MS. Responsibility for authorisation of clinical trials remains a national competence.

- **Consent process** – Essentially the same but with the addition of “broad consent” to allow data from a trial to be used outside of the protocol for the specific trial. Rules also added for trials in emergency situations and simplified consent for cluster trials.

- **Conduct of the trial** – New requirements for notification through the portal of start, end, temporary halt and early termination of the trial. Sponsors must report “serious breaches” of GCP.

- **Reporting requirements** – Greatly simplified as all interaction by sponsors with both NCAs and ethics committees takes place through the single EU portal and only needs to occur once to reach all concerned institutions.

- **Risk adaptation** – Allows consideration of the characteristics of the trial to determine the level of adaptation to be applied to such areas as monitoring, trial master file, traceability of investigational medicinal products (IMPs), safety reporting. These characteristics include whether the trial is low-interventional, the objectives and methodology of the trial and difference from normal clinical practice.

- **Transparency** – Significant change to the policy on public access to information on clinical trials contained in the EU database, with the default being that all data will be publicly accessible unless certain confidentiality criteria are met. Also, only data from trials previously registered on a public registry can be used to support CTAs.

- **Safety reporting** – Essentially similar requirements but with a new web-based reporting form and database for serious, unexpected, suspected adverse reactions (SUSARs) and a new central database for annual safety reports. MS will have to jointly assess these reports.

- **Annexes** – Much of the guidance associated with the Directive and included in EudraLex Volume 10 has been incorporated into the text of the Regulation or added into one of six Annexes. This changes their status to legal requirements. These Annexes may be changed by the Commission through the adoption of Delegated Acts, simplifying the mechanism to make changes in the future.

- **Commission controls** – The Commission has a new supervisory role in relation to MS compliance with the Regulation and third country compliance with principles equivalent to the Regulation.

### Implementation of the Regulation

The Regulation differs from the current Directive in that as a Regulation it applies directly in all MS without the need to transpose into national legislation, and so ensures a much greater degree of harmonisation when implemented. While this might suggest that it will be relatively easy to transition from the Directive to the Regulation this is in fact far from the case, and there is a great deal of work required at the EU and national levels, by regulators, ethics committees and the research community, to prepare for this change.

At the EU level there are a number of collaborative groups involved in preparing for the Regulation (see Table 1). These are largely focused on providing MS input and support to the European Medicines Agency (EMA) and Commission activities, as well as coordination of the MS preparations nationally.

At both the EU and national levels, the work falls broadly into three categories:

- Process and IT systems development
- Development of supporting legislation
- Communications and training.

### EU level

#### Process and IT systems development

Article 80 of the Regulation states: “The Agency shall, in collaboration with the Member States and the Commission, set up and maintain a portal at Union level as a single entry point for the submission of data and information relating to clinical trials in accordance with this Regulation. The EU portal shall be technically advanced and user-friendly so as to avoid unnecessary work.

Data and information submitted through the EU portal shall be stored in the EU database.”

Full functionality of this EU portal and database is essential to be able to implement the Regulation and so this activity is absolutely critical, and will dictate the rollout of all other activities. The Regulation will apply six months after publication by the Commission of the results of an independent audit of the system, in the *Official Journal of the European Union*.

The EMA set up a series of working groups and subgroups (Table 1) to look at and document the processes and system requirements for the portal and database in early 2014. A high level Functional Specification for the system was agreed by the EMA Management Board in December 2014 and work has continued since then on detailed business use cases which will define the full functionality of the final system; development is expected to start in Q3 of 2015.

Detailed timelines for full delivery of the system are still being finalised but it is anticipated that the audit will be initiated late in 2016 and application of the Regulation will occur during 2017. In parallel, other teams within the EMA, supported by MS sub-groups, are working on developing the safety databases for SUSARs and annual safety reports, a data-warehouse capability and EudraCT and Registry legacy processes.

**Transparency.** During the negotiation of the text of the Regulation by the co-legislators, transparency became a very politically sensitive topic with an emphasis on much more public access to data, documents and results of clinical trials.

Under the current legislation the EU clinical trials database (EudraCT) was created in May 2004, and contains the application form data for all clinical trials undertaken in the EU since then, but remains accessible only to the competent authorities of the MS, the EMA and the Commission. In 2011 a limited subset of data from EudraCT, for all trials held in the database except adult Phase I trials, were made publicly available through the creation of the EU Clinical Trials Register. This was further enhanced in 2014 with the ability to publish a summary of trial results on the Register within 12 months of trial completion.

Article 81 of the Regulation describes the creation of an EU database and states in paragraph 4:

“The EU database shall be publicly accessible unless, for all or part of the data and information contained therein, confidentiality is justified on any of the following grounds:

(a) protecting personal data in accordance with Regulation (EC) No 45/2001;
(b) protecting commercially confidential information, in particular through taking into account the status of the marketing authorisation for the medicinal product, unless there is an overriding public interest in disclosure;
(c) protecting confidential communication between Member States in
relation to the preparation of the assessment report;
(d) ensuring effective supervision of the conduct of a clinical trial by Member States.”

This database will hold all of the documents and information provided by the sponsor for trial authorisation for all trials including Phase I, as well as the assessment report, substantial modification information and a summary of results. All of this information will be accessible to the public if and when none of the criteria in (a)–(d) above apply. Since some of the criteria may apply differently at different times throughout the drug development cycle it is important to have clear rules that can be applied in a consistent way on “what” and “when” to provide public access. The challenge is to get the balance right between the need to provide open and transparent access to the database and protecting the legitimate interests of innovators and researchers conducting their activities in the EU. A detailed policy on this area is currently under development by the EMA, European Commission and MS as part of the development of the EU portal and database.

A further development in the Regulation is that only data from trials previously registered in a public registry, including Phase I, will be able to support a CTA in the future. In addition, clinical study reports (CSRs) from trials used to support marketing authorisation (MA) applications will need to be published by the MA applicant on the database within 30 days of the MA decision, whether positive, negative or withdrawn. This was considered a very important part of the transparency provisions and MS are required to incorporate penalties into their national legislation to deal with non-compliance with this requirement.

### Development of supporting legislation
There are a number of areas where it is intended that the Regulation will stand alone and not refer...
to other legal texts, but will require additional legislation to achieve this. There are two principal areas affected, good manufacturing practice (GMP) and GCP:

- **GMP** – The Commission is empowered by the Regulation to specify the principles and guidelines of GMP, and the detailed arrangements for inspections, for ensuring the quality of IMPs, through the adoption of a Delegated Act. These are defined as non-legislative acts of general application to supplement or amend certain non-essential elements of a legislative act.

  The Commission has worked with its Clinical Trials Expert Group and other key regulatory stakeholders (such as GMP and GCP inspectors) to develop an initial draft text for a Delegated Act on GMP which is expected to be available for public consultation in Q3 of 2015.

- **GCP** – Similarly the Commission is empowered through the adoption of an Implementing Act to provide the detailed arrangements for inspections and inspections procedures including the qualifications and training of inspectors. The intention was to base the new implementing regulation on the provisions of the currently applicable Directive 2005/28/EC (GCP Directive).5

  Again the Commission has worked with its Clinical Trials Expert Group and others to prepare an initial draft text for the Implementing Act, which is expected to be available for public consultation in Q3 of 2015.

- **Other guidelines** – Current implementing guidance documents available in EudraLex Volume 10 – such as CT1 (authorisation process)6 and CT3 (safety reporting)7 – have largely been incorporated into the text of the Regulation and its Annexes. Where there remain gaps which would benefit from additional guidance, the current thinking is that these can be addressed through frequently asked questions (FAQs). Work has already been started to develop and build on a list of FAQs by the Commission in collaboration with its Expert Group.

**Communications and training.** The Clinical Trials Facilitation Group (CTFG) is planning to coordinate the sharing of best practice and training of MS representatives on three levels:

1. To ensure a common and consistent level of understanding of the Regulation across all the NCAs in the EU
2. To prepare and train assessors across MS to work together under the new legislation, both for CTA assessment and for assessment of safety reports
3. To involve ethics committee members in the MS in developing their knowledge and understanding of the Regulation and developing best practice approaches to working with it.

This activity is being worked up in conjunction with the newly created EU Network Training Centre and will roll out during 2016/17.

It is anticipated that following the audit of the EU portal and database, a version of the system will be made available by the EMA to MS and the public for training purposes, but also to allow interfacing and process development.

**National level**

**Process and IT systems development.** The EU portal and database being developed by the EMA will provide a conduit for sponsors to make applications for all clinical trial authorisations in the EU and give MS access to the associated information and documentation. Discussions are currently continuing on many of the technical aspects of how the interface between the EU and MS systems will look and operate.
clear, however, that in many MS new processes and ways of working will need to be established to allow the NCAs and ethics committees to liaise and jointly assess aspects (eg, Part 1) of the CTA. It is also clear that for many of the MS, particularly the ones with the higher numbers of CTAs, new IT systems will need to be developed nationally to facilitate this interaction. Activities to support these developments are now underway in almost all MS, and experience gained nationally is being shared through the CTFG.

In the UK, discussions between the Health Research Authority (HRA) which oversees and coordinates ethics committees and the MHRA, the competent authority, have begun, with several workshops to look at process and system requirements for future working under the Regulation. A work programme is being developed to take all of these aspects forward.

**Development of supporting legislation (UK example).** The Regulation is directly applicable in all MS but some domestic legislation is required to support the functioning of the Regulation and to make use of the flexibilities that the Regulation offers MS.

In the UK, the Medicines for Human Use (Clinical Trials) Regulations 2004\(^1\) and all associated amendments will need to be repealed and new domestic legislation developed to replace it. It is anticipated that the new UK Clinical Trials Regulations will become part of the Human Medicines Regulation 2012.\(^2\) Provisions in the following areas are needed:

1. Ethics Committees (Article 2.11, Article 4)
2. Appeal mechanism for decisions on CTAs (Articles 8(4), 14(10), 19(2), 20(7) and 23(4))
3. Legally designated representative for incapacitated persons and minors (Articles 2(20), 31, 32 and 35)
4. Incapacitated subject (Article 2(39), Article 31)
5. Minors (Article 2(18), 32)
6. Interview prior to informed consent (recital 30, Article 29(2)c)
7. Investigator (Article 49)
8. Importation of unauthorised auxiliary medicinal products (Article 59(3))
9. Authorisation of manufacturing and import (and inspection) (Article 61)
10. Fees (Articles 86 and 87)
11. IMPs free of charge (Article 92)
12. Sanctions, penalties and inspections (Article 94 (penalties), Articles 78, 61(6), 63(4) (inspections)).

Initial drafting of the text has started and it is anticipated that this will be ready for a public consultation at the beginning of 2016. The text will then need to be amended and finalised for Parliamentary approval later in 2016. The “entry into force” date of this new domestic legislation will need to be linked to the day of application of the Regulation.

**Communications and training.** It is anticipated that in most MS the NCA will take the lead in ensuring that their research community and other national stakeholders are aware of and trained on the Regulation in preparation for its application. The activities of the CTFG at EU level are designed to train all MS and share best practice to achieve a consistent approach to this.

In the UK, work has started to develop a communication plan to roll out over the next few years which will utilise a range of media and approaches to ensure the new regulatory requirements are understood by as many of the research community as possible before the application date and in support thereafter.

**Timelines.** The Regulation was published on 27 May 2014, entered into force 21 days later on 16 June 2014 and can apply no earlier than 28 May 2016. While significant progress has been made in developing and agreeing business requirements for the EU portal and database system, detailed planning is still ongoing. The actual date of application of the Regulation will depend on the availability of the full functionality of this system. It is currently anticipated that the audit will be initiated late in 2016. A successful outcome will be agreed by the EMA Management Board and announced through a Commission publication in the **Official Journal of the European Union**. The process of audit, agreement and publication is expected to take approximately six months and the application of the Regulation will follow six months after this publication. It can therefore be anticipated that the application of the Regulation is likely to be in late 2017.

**Transitional arrangements.** Before the date of application of the Regulation only the current legislation, the Directive, may be used for CTAs. From the date of application for a period of one year, either the Directive or the Regulation may be used to make applications, that is either using the EudraCT system or the new EU portal and database. After that one-year transitional period only the Regulation may be used but trials started under the Directive may continue using that legislation for a further two years, after which they will need to be converted to operate under the Regulation. This is represented diagrammatically in Figure 1 (see previous page). After that point, the EudraCT systems will become legacy systems and will not be available for any further use. Detailed planning on how this transition will be managed practically has still to be completed.

**Summary**

The Regulation offers those wishing to conduct clinical trials in the EU a much more streamlined, efficient and consistent regulatory environment and it should make the EU a more attractive place to conduct clinical research. There are some significant challenges for regulators to put in place processes and systems to enable this, and in particular to ensure that from the date of application of the Regulation the environment is fully functional and reliable. This article outlines the key areas that must be, and largely are being, developed by regulators and other key stakeholders in preparation for the Regulation but at this point in time much still remains to be done.

**References**