The New EU Clinical Trial Regulation: A First Impression

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The new EU Clinical Trial Regulation was officially published on 27th May 2014, (Regulation (EU) No 536/2014). The Regulation will come into effect no sooner than 28th May 2016 and at least six months after the submissions portal through which all applications are to be made is declared fully functional by the EMA/Commission. The regulation will replace the current EC directive 2001/20, which has governed clinical trials in the European Union for the last 10 years.
Why a New Regulation?


The problem with this and many EU directives intending to harmonise rules across Europe is that they are subject to national implementation, which means that there are different interpretations and systems in each member country. Therefore, multiple applications of nearly identical dossiers have to be made in each country concerned if more than one is country is involved, which leads to multiple assessments and then to divergent decisions, resulting in uncertain timelines and outcomes.

The new legislation is an EU Regulation and so applies directly in all member states (MS). Notionally, this provides an overall ‘shorter’ authorisation time for multi-state clinical trials. Assuming the submission portal is completed as planned the regulation will affect applications from mid-2016, with a transition period of a year when both systems will run in parallel.

Scope of New Regulation

The new Regulation will apply to all clinical trials within the EU but not to ‘non-interventional’ studies. There are differences in the definitions of the terms, ‘clinical study’ and ‘clinical trial’, which define ‘non-interventional studies’ as being distinct from clinical trials.

The distinctions that makes a clinical study into a clinical trial and so covered by the regulation are:
- In a non-interventional study the patient is usually being treated within normal clinical practice
- In a non-interventional study the decision to prescribe a treatment is taken before entry into the study
- The above would not be non-interventional and a clinical trial.

The definition of a low intervention trial, which is a clinical trial where:
- The investigational medicinal products (IMPs), excluding placebos, are authorised according to the protocol of the clinical trial are:
- The IMPs are used in accordance with the terms of the marketing authorisation; or
- The use of the IMPs is evidence-based and supported by published scientific evidence on the safety and efficacy of those IMPs in any of the MS concerned; and
- The additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any MS.

An auxiliary medicinal product is defined and covers products used in a clinical trial that are not part of the investigation such as rescue therapies or challenge agents, as distinct from placebos or comparator products.

The requirement for non-EU sponsors to have a legal representative is no longer required (national rules will decide).

Clinical Trial General Principles

A clinical trial may be conducted only if: the rights, safety, dignity and well-being of subjects are protected and prevail over all other interests and it is designed to generate reliable and robust data. This is not much of a change; however, the inclusion of the protection of the ‘dignity’ of the subject will be an interesting issue to document.

The clinical trial authorisation process will be subject to scientific and ethical review by the competent authorities; with Independent Ethics Committee scrutiny under national legislation but the ethics review timings to be aligned with timelines for overall authorisation.
Part I Assessment

During the Part I assessment, the RMS will prepare an initial draft assessment report that is circulated to the CMS for comment and a coordinated review; the RMS then modifies the report and if complete, issues a final assessment report to the sponsor. Between the validation and reporting date (45 days), the RMS (only) may request further information from the sponsor, taking into account issues raised by the CMS. If further information is requested from the sponsor, the reporting period may be extended by 31 days (76 in total); this allows up to 12 days for the sponsor to respond to questions, 12 days for a coordinated review and seven days for the RMS to finalise the assessment report.

Part I Timelines

Figure 1. At the end of the Part I assessment, the RMS will issue an assessment report with a conclusion that the conduct of the trial is acceptable, acceptable subject to certain conditions or that it is not acceptable. A conclusion that a trial is not acceptable by the RMS is deemed to be the conclusion of all CMS.

Part II

The assessment of Part II is a national assessment involving one application. This information includes much of what is normally considered by the Ethics Committee. The Part II assessment will be conducted at the same time as the Part I assessment if the two parts are submitted together.

Part II Timelines

Figure 2. The assessment will be conducted by each MS individually and is a decision on: compliance with informed consent requirements; arrangements for reward or compensation of subjects/investigators; arrangements for recruitment; compliance with Directive 95/46 (data protection); suitability of the sponsor’s/CRO’s investigators to conduct the clinical trial; suitability of sites; adequacy of damage compensation system/insurance; compliance with rules on collection and storage and future use of biological samples.

These aspects (as well as others) are usually considered by the Ethics Committee. It seems that the Part II submission will be instead of or in addition to any Ethics Committee submission, as it is purely national. If the Part II submission is made in parallel with the Part I, the timing will be such that the EC decision cannot wait until the Part I is final, as the MS has to give a final decision on Part II within the same overall timetable or within five days of the Part I reporting date if that is later. This may be a major challenge for Ethics Committees and national competent agencies to coordinate.

‘Between the validation and reporting date (45 days), the RMS (only) may request further information from the sponsor, taking into account issues raised by the CMS.’
Overall Decision by each Member State

A single national decision reflecting the competent authority position and ethics is to be notified to the applicant via the portal indicating whether the trial is authorised, authorised subject to conditions, or not authorised: within five days of the Part I reporting date or on the last day of the Part II assessment (whichever is later).

The decision from each country will indicate whether the conclusion of the Part I assessment is acceptable or that it does not accept the Part I assessment report (only permitted in certain circumstances) and its decision on Part II if it accepts Part I.

If a CMS does not issue a decision within five days of the reporting date of the Part I assessment or the end of the Part II assessment period (whichever is later), then the decision is that given in the final assessment conclusion of the RMS. So a non-response within the timetable where a Part I assessment is positive results in a tacit approval.

If a CMS does not accept the Part I decision then that country cannot participate in that trial protocol – a separate application for another study with a new protocol and clinical trial number and study report would be required. The circumstances in which a CMS country can reject a Part I assessment if it disagrees with the conclusion of the RMS are limited. A CMS may not ask for further information on Part I after the reporting date.

Overall Timelines

Figure 3. So, if submitted together the Part I and II assessments must be completed within 76 days, and if Part I takes the whole 76 days to complete then the decision must be given within five days (so up to 81 days after validation). As validation may take 10 to 25 days, then the overall timings may be between 60 and 106 days; decisions could be quicker if Part I was concluded sooner than 45 days.

Substantial Amendments

- The Regulation sets up a scheme for approval of substantial amendments to Part I. This is a similar procedure to the Part I assessment, with up to 38 days for assessment after validation, +31 days for extension if questions are raised and a decision within five days of the assessment report.
- For substantial amendments to Part II (including new sites/investigators), a similar 38-day timeframe (plus extension for questions) is allowed.
- Detailed guidance on what constitutes a substantial amendment may be required.

Notifications via the Portal

The sponsor/applicant is required to notify via the portal within 15 days, each country at each of the following, start of recruiting, first patient first visit, end of recruiting, last patient last visit (LPLV) final end of trial (LPLV last country), suspension, temporary halt and early termination.

Other Notifications Required

Detailed suspected unexpected serious adverse reaction (SUSAR) reporting via the EMA database, annual safety report(s) and all third-country inspection reports.

Trial Management Changes

- There are some minor changes to the definitions of informed consent. Informed consent is required to be via an interview to gain consent, giving the subject time to reach a decision.
- A record of consent given by the subject is to be written, and also dated and signed by the person conducting the interview and if applicable their patient/legal representative.
- Special informed consent is required for minors, incapacitated patients, breast feeding or pregnant women, cluster trials (in one MS only and low-intervention studies) and in emergency situations.
- Low intervention studies have some other more limited data collection and serious adverse event reporting requirements.
- Each trial will have a unique EU trial number (currently Eudract number).
- Access for citizens via the EU Clinical Trial Database – results will also be available in a lay summary (subjects must be told how to find the results in the EU database – and as far as possible when the summary is available). Each medicinal product and active substance is required to have a unique product number before submission of the first clinical trial.
- Adverse event reporting to the EMA is required via a module of the Eudravigilance database and SUSARs are required to be reported within specified timelines. Annual safety reports are required via the Eudravigilance database. The agency will forward these reports to the MS.
- Manufacture and import and QP release requirements and labelling requirements are specified.
- The sponsor must monitor and conduct the clinical trial in compliance with the Regulation and GCP. In addition, sponsors must report serious breaches of GCP within seven days.
- Storage, traceability, return and destruction of the IMP must be tracked. The clinical trial master file must be kept for at least 25 years, be readily available and accessible.
- All previous trial data in the submission must be registered on a database that is a primary or associate register to WHO ICTRP – e.g. Eudracit or clinicaltrials.gov.
- A requirement for provision of damage compensation is required either as – insurance or national scheme.
- The regulation provides the usual powers for suspension, revocation or modification of the clinical trial approval by the member states.
Other Powers and Responsibilities

Other powers and responsibilities that are specified include: inspections, EU database, EMA submissions portal, a clinical trial advisory group is formally established, fees – one payment per activity per MS, data protection requirements for investigators as well as subjects. A summary of results must be submitted to an EU database within one year of completion, including a summary of results for the lay person.

Timetable for Implementation

The Regulation will become effective six months after the EU portal is declared to be fully functional and no earlier than 28th May 2016. There will be a transition period, which will allow anything submitted before the effective date to continue under the existing Clinical Trials Directive for three years. There will be at least a one year overlap of the two systems, so submissions under the current system will be possible until at least 28th May 2017 and these ongoing trials can be governed by the existing directive until 36 months after the effective date or 28th May 2019 if the effective date is before 25th November 2015.

Potential Benefits

■ Approval may be quicker overall, possibly after 60 days; however, it could take up to 106 days and even longer when more time is allowed for ATMP products, etc.
■ There will be a single scientific assessment and questions
■ The Ethics Committee review will be required to be performed within same national timetable – although it remains unclear how this will work
■ A single submission via the portal and responses via the portal.

Potential Issues

■ Compatibility of MS IT systems – how will this work?
■ Extra documentation for some countries - can original signatures/paper copies be avoided?
■ EC approvals have to be gained nationally but within the same timeframe – will the Ethics Committees accept the Part II information only; if not, what else will be required?
■ Workloads for RMS – are a small number of countries likely to act as RMS for the majority of applications, as is currently the case for the decentralised procedure?
■ Will current flexibility in timings for responding to questions be lost? – 12 calendar days is very limited, should the applicant be able to ask for a clock stop?
■ A considerable amount of the detail regarding the submission document requirements is still unclear.

So, overall, a potential improvement over the current Clinical Trials Directive is possible but a considerable amount of the detail needs to be clarified within the next two years if it is to be a success.

REFERENCES

Electronic copy accessed 30th May 2014 (English)

Biographies

Mike is an expert regulatory professional with extensive experience in all aspects of regulatory affairs in a wide range of development, operational and consultancy roles, seeing products from development to production, launch and ongoing support and maintenance.

Mike has over 30 years of regulatory expertise in the pharmaceutical industry from small and mid-sized pharmaceutical companies to regulatory consultancy in CROs.

As Head of Regulatory Affairs at GFA Mike provides strong strategic and specific advice to clients and supports and manages the regulatory team at GFA. He joined GFA in April 2011 following over 12 years in regulatory consultancy as a Consultancy Manager and Director of Regulatory Consulting. Prior to that he held posts as Head of Regulatory Affairs in a small development company developing modified release dosage forms and earlier in a number of regulatory and development roles for a mid-sized pharma company Fisons Pharmaceuticals in the UK.

Mike has broad expertise in all aspects of regulatory affairs and has worked on products from novel peptides, vaccines and new chemical substances to generics and borderline pharmaceuticals and food supplements.

Mike is an honours graduate in Chemistry from the University of Sheffield, a member of TOPRA the European regulatory professional organisation and a Professional Member of the Royal Society of Chemistry (UK).

MIKE BATEMAN

Céline is Regulatory Affairs Executive at GFA and an experienced academic researcher with a rich background in Molecular Biology and Cancer Genomics. She spent many years at the University of Cambridge, working on the characterisation of genomic rearrangements occurring in breast cancer cells. She also participated in a Europe-wide project studying spontaneous tumours in purebred dogs as a model for genetic factors in human cancer. Céline has been in regulatory affairs consultancy for two years, concentrating on gene therapies and other biotech products.

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