The new Clinical Trial Regulation (EU) No 536/2014 was adopted on 16 April 2014 and published in the Official Journal on 27 May 2014. When it comes into full effect, it will bring a revised set of rules for the conduct of clinical trials in Europe with a focus on modernisation, streamlined processes and increased public access to information. Unsurprisingly, the interest of the research community is high and it is hoped that the new environment will boost conduct of clinical trials in the EU. Aimed at pharmaceutical industry sponsors, updates about the implementation are discussed together with some advice to help prepare more efficiently for this new regulatory framework.

Implementation

According to the EMA’s latest press release (17 December 2015), the timeframe for development of the IT platform (EU submission portal and database) has been extended and will be available for an independent audit by August 2017. If the outcome is positive, the Regulation will come into effect at the latest by October 2018. From then on, the portal and database will be operational for sponsors and EU member states (MS) to use for all new clinical trial applications; in addition, the information from the database will be publicly available. For a period of one year after the Regulation has been implemented, clinical trial applications may be submitted using either the old Directive 2001/20/EC or the new Regulation, followed by a period of two years whereby trials that had started under the Directive will need to be converted to operate under the Regulation by approximately 2021.

At present, collaborative groups are working on the detailed planning and business requirements for the EU portal and database. In parallel, national IT tools and legislation are under preparation so that adequate interfaces with the EU system are achieved. It has been recognised that one of the key factors for successful implementation will be establishing a communication strategy and training for all stakeholders. Therefore, the Clinical Trial Facilitation Group has been granted the leading role in training and sharing best practice with all MS (via the EU Network Training Centrum), while national agencies are expected to provide updates to the local research community. In order to keep up with the technical progress and international regulatory developments in clinical research, the Regulation empowers the European Commission (EC) to make changes in the six accompanying Annexes through the adoption of Delegated Acts. Implementation responsibilities for the Regulation will be shared between the EMA, EC and Parliament, and sponsors will need to monitor these tripartite arrangements.

At this stage of implementation, industry and academia are heavily involved in providing comments on draft proposals for specification documents. This external engagement has to be followed by effective internal information flow by, for example, setting up internal communication plans accompanied by
‘road shows’ to raise awareness. Sponsors should put in place dedicated cross-functional groups consisting of high-level teams with ultimate functional responsibility, and operational teams performing initial impact analysis and subsequently proposing changes to company processes. Empowered leaders who are able to escalate concerns and resource needs are critical in the coming months.

Submission and Approval Process

One of the major novelties brought by the Regulation is the streamlined authorisation procedure via a single entry point: the EU portal and database. An application dossier will be evaluated by national scientific and ethical review in order to ensure one single assessment outcome per MS. Each trial will receive a unique EU trial number and each medicinal product and active substance will be registered by a specific product number.

The CTA dossier will consist of two parts, with Part 1 containing general information on the trial (such as protocol, investigator’s brochure (IB), investigational medicinal product dossier (IMPD), or labelling) and Part 2 comprising of information regarding sites, patient-specific documents and study setup. Part 1 assessment will be coordinated by a reporting member state (RMS) with concerned member states (CMS) providing a consolidated feedback in a single Part 1 assessment report. Part 2 will comprise of a national review with parallel independent ethical committee assessment.

The timelines are strictly defined: a validation period of 10-25 calendar days (including 10-day clock stop for additional information), an assessment period of 45-76 days (including 12-day clock stop for response to questions) and five days for notification of decision. An RMS can extend assessment time by 50 days for advanced therapies and products derived from rDNA technology. Failure of a CMS to provide comments in time will result in automatic approval (the new concept of tacit approval), while silence from sponsors will lead to automatic withdrawal of the application from all CMS. Resubmission is possible but this will be considered as a new application.

The process for substantial modification of either part of the dossier is similar to the initial procedure (45-76 days), as is the timeframe to add an MS (52-83 days). These modifications can only be done after the decision on initial submission has been made. It is obvious that the new procedure calls for rigorous quality control and careful planning during the trial start-up and country selection process in order to avoid delays. The review timelines can be shorter and some MS have already indicated that for single-centre, single-country trials, current review timelines will be applicable. Thus, understanding MS requirements is going to enable adequate dossier preparation, as well as allow strategic decisions to be made about the choice of...
ICT

allow data from a trial to be used outside the protocol for 'substantial amendment'; addition of 'broad consent' to rules for lower-risk studies, 'substantial modification' instead of 'low-intervention' clinical trials to allow simplified definitions and clarifications have been introduced. Some of these are: 'low-intervention' clinical trials, new requirements for submission of annual safety reports and all third country inspection reports to the EU database, hosted by the EMA. Sponsors must also notify serious breaches of Good Clinical Practice within seven days and commence corrective actions promptly.

To guarantee compliance, sponsors will need to put in place relevant measures – for example, IT systems for notifications – as well as defining accountability and communication flow from local affiliates to global entities. Such a system will allow comprehensive central EU supervision to ensure all necessary information is submitted to the EMA portal in a timely manner.

### Transparency Issues

Following extensive public consultations, the recently endorsed addendum 'Appendix on disclosure rules to the functional specifications documents' (EMA/228383/2015) describes the practical implementation of the transparency rules. The public will be able to access vast details on each trial, including major characteristics, the start and end of recruitment, its end date and substantial modifications. A summary of the results and lay summary must be published within 12 months after the end of trial, but the new transparency addendum has now further specified exception rules laid in the Regulation – for instance, personal data, classification of commercially confidential information, confidential communication during the assessment, and protection of the supervision of clinical trials by an MS. A need for a balanced approach as to what will be publicly available at what point in time has been recognised in order to protect public health, while acknowledging legitimate economic interests of sponsors. The following categories of clinical trials have been

### New Definitions and Notification Requirements

Although the Clinical Trial Regulation, as with the current Directive, applies only to interventional trials, several new definitions and clarifications have been introduced. Some of these are: ‘low-intervention’ clinical trials to allow simplified rules for lower-risk studies, ‘substantial modification’ instead of ‘substantial amendment’; addition of ‘broad consent’ to allow data from a trial to be used outside the protocol for a specific trial; ‘legally designated representative’ for minors and incapacitated adults; ‘auxiliary medicinal product’ instead of ‘non-investigational medicinal products’; and ‘co-sponsors’.

The Regulation also requires a comprehensive notification schedule with an effective automated notification system via the EU portal. The following notices to each concerned MS will need to be made within 15 days of occurrence: start of recruitment, first patient and first visit in each country; end of recruitment, last patient and last visit in each country; final end of the trial; suspension; temporary halt; and early termination. All of these terms need definitions in standard operation procedures to enable compliance to be monitored. Other notifications, such as suspected unexpected serious adverse reaction (SUSAR) reporting to the EudraVigilance Clinical Trial Module, carry on as normal – although there are new requirements for submission of annual safety reports

| Table 1: Timing of publication of data and documents |
|--------------------------------------|--------------------------------------|--------------------------------------|
| **Category 1:** Phase 1, bioequivalence and bioavailability trials | **Category 2:** Phase 2 and 3 trials | **Category 3:** Phase 4 and low-intervention trials |
| Protocol, subject information sheet, IMPD safety and efficacy, IB | Time of decision on the trial, but sponsors may opt to defer this up to time of MA or up to seven years after the end of the trial | Time of decision on the trial, but sponsors may opt to defer this up to the time of MA or up to five years after the end of the trial |
| Clinical trial results summary, lay person summary | 12 months after the end of the trial or later if scientifically justified (Article 37(4) of Regulation 536/2014 (1)) * | 12 months after the end of the trial or later if scientifically justified (Article 37(4) of Regulation 536/2014 (1)) * |
| Sponsors may opt to defer to a maximum of 18 months after the due date (usually 12 months after the end of the trial unless opted to delay by seven years). In total, a potential maximum of 30 months after the end of the trial or until time of MA | 12 months after the end of the trial or later if scientifically justified (Article 37(4) of Regulation 536/2014 (1)) * | 12 months after the end of the trial or later if scientifically justified (Article 37(4) of Regulation 536/2014 (1)) * |
| Clinical study report | 30 days after the marketing authorisation decision (authorisation or refusal of MA application) or 30 days after withdrawal of the application by the applicant |

*Note: six months for paediatric trials. Section Q of IMPD will not be made public. If summary of product characteristics is referred to, instead of IMPD Section Q being submitted, that reference will be made public.

RMS to benefit from a high-quality assessment. The need for sponsors to install effective quality systems through cross-functional teams is paramount to comply with tight timelines, learn from errors smartly and monitor MS performance.
identified in order to simplify and standardise the automated release of data in a clinical trial dossier (see Table 1):

- Category 1 (non-paediatric, pharmaceutical development) clinical trials: Phase 1 trials in healthy volunteers and sometimes patients; bioequivalence and bioavailability trials; biosimilarity and equivalence trials for combination products
- Category 2 (therapeutic and confirmatory) clinical trials: Phase 2 trials investigating therapeutic safety and efficacy or potential dose regimes; Phase 3 trials for confirmation of safety and efficacy
- Category 3 (therapeutic use) clinical trials: Phase 4 (post-marketing trials); low-intervention trials

The timing of publication is based on the key milestones of a clinical trial, with the possibility of opting for deferral for up to seven years after the end of category 1 trials and up to five years after the end of category 2 (see Table 1, page 16). The publishing of urgent safety measures and SUSARs occurring during category 1 can be deferred until summary results are made public, as long as these matters are dealt with by using adaptive study design or via substantial modifications.

These periods of five (or seven) years are considered appropriate as they ensure that adequate up-to-date IBs and IMPDs can be submitted with confidence to the EU portal, providing sponsors sufficient time to reflect how publication affects their wider interests. However, information is inevitably going to be made public even for those IMPs that will never achieve marketing authorisation. This is a very welcome step from the new Regulation, as it addresses previous concerns that sponsors were not learning from each other about the reasons why many products fail during development.

Since much more information is going to be in the public domain, sponsors will need to establish publication plans, and incorporate internal quality audits of clinical trial documentation (submission dossier, clinical results summary, lay summary and clinical study results) so that they are confident about what is being disclosed. Processes must synchronise both regulatory and financial communications so that investors are kept fully informed.

Conclusion

The new regulation will undoubtedly bring necessary innovation and modernisation to clinical trial conduct in the EU by introducing a single EU portal and database, unified application dossier, coordinated application assessment and single opinion per MS, as well as increased transparency. It will be critical that the time until its full application is used efficiently by all stakeholders to carefully plan and design processes and IT systems to support this new way of working.

Acknowledgement

We would like to thank Paul Strickland at Strickland Quality Assurance Ltd for his valuable advice.

References


About the authors

Olga Björklund has been a Senior Consultant at NDA Group since 2014. She has worked in the pharma industry since 2009 – within global regulatory affairs and project management with AstraZeneca; and global clinical study start-up at ICON. Olga holds a PhD in Neuromolecular Pharmacology and an MSc in Pharmacy.

Dr Brian Edwards is Principal Consultant in Pharmacovigilance and Drug Safety at NDA Group. He is a General Medical Council-registered physician with previous experience in hospitals, renal medicine and clinical research. Brian joined NDA in 2007 and specialises in pharmacovigilance, quality management and all aspects of safety compliance, risk management, Qualified Person for Pharmacovigilance Services and clinical trial safety.

Email: info@ndareg.com