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New and Approved

The much-anticipated EU Clinical Trials Regulation aims to lower administrative burdens, streamline processes and increase transparency. While this may make Europe a more attractive destination for clinical research, it also poses significant challenges for the pharma industry

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New EU legislation governing the regulation of clinical trials in Europe has been enacted to make the region a more attractive destination for clinical research. It aims to reverse the decline in the number of studies on human medicines being carried out, while ensuring high standards of patient safety are maintained. Although the overall aim of the Regulation is to harmonise processes and increase efficiency across EU member states, its implementation is also likely to pose some significant problems for the pharmaceutical industry.

On 27 May 2014, the EU Clinical Trials Regulation 536/2014/EU – repealing the EU Clinical Trials Directive 2001/20/EC – was published in the *Official Journal of the European Union* (*OJ*) (1). Its key objective is to simplify and streamline the procedures for the submission of an application dossier for the authorisation of a clinical trial, especially in studies carried out in more than one EU member state.

One of its aims is to avoid the multiple submission of largely identical information by replacing the current national application and reporting procedures with single submissions to all relevant EU member states via a single reporting portal. Member states are also encouraged, though not obliged, to accept single language dossiers. Furthermore, sponsors and other stakeholders will be able to rely on the provisions of the Regulation directly, thereby minimising divergences of approach among different EU member states.

The earliest possible application of the Regulation is 28 May 2016 (two years from the *OJ* publication). However, it will not come into force until six months after notification, via the *OJ*, that the EU portal and database are fully functional – confirming the fundamental importance of this IT infrastructure to the delivery of the new clinical trials regime. Transitional arrangements will then apply in respect of study applications made prior to the applicable date.

Regulatory Scope

The Regulation has the same scope as the previous Directive, which it replaces, and applies to all clinical trials conducted within the EU for medicinal products – with the exception of non-interventional studies. It introduces the concept of a low-intervention clinical trial (LICT) – one which involves further investigation or repurposing of a medicine that has already been authorised, and where any extra diagnostic or monitoring procedures pose no more than minimal additional risk to the safety of the subjects concerned, compared with normal clinical practice in the relevant EU member state.

There are two main elements:

Firstly, the clinical trials authorisation procedure will involve a single application made by the sponsor, in respect of all target member states, through a single submission portal operated by the EMA, whether for single-centre or multi-centre studies. The sponsor nominates a 'reporting member state', although each country concerned must authorise the application. This procedure has similarities with the decentralised one for marketing authorisations for medicinal products according to Directive 2004/27/EC. Similar arrangements apply for substantial amendments and extensions of studies to sites in additional member states.

Secondly, the application procedure comprises two parts:

- Part one, which is led by the reporting member state, involves assessment of the therapeutic and public health benefits of the medicine; the potential risks for trial subjects; the investigator's brochure and compliance with manufacturing; and import and labelling requirements
- Part two, which is assessed by each concerned member state in respect of its own territory, includes assessment of compliance with the requirements for informed consent and data protection; compensating (remunerating) subjects and investigators; the recruitment of subjects; the suitability of trial sites and the investigator team; damage compensation; compliance with rules on the storage of biological samples; and ethics committee review

Since it is not necessary to complete applications for parts one and two simultaneously, sponsors may opt to complete part one first, and then apply for part two authorisation within the two-year period allowed, or choose to add additional sites in other member states at a later date.

The key features of the new Regulation include:

- A single EU database, also operated by the EMA, containing all of the information submitted via the portal. Subject to certain exceptions – for example, personal data, commercially confidential information of the sponsor, and communications among concerned member states – the database will be publicly accessible and searchable. The sponsor will have an ongoing updating obligation with respect to any information it has filed
- A target overall timeline – from submission of the application dossier by the sponsor to authorisation of the trial – of just 60 days (110 for advanced therapy or biotechnology products). Extensions to this timeline are only possible in limited circumstances, though Q&As from member states can extend the authorisation timeframe to up to 106 or 156 days, respectively
- A concerned member state can only disagree with part one assessments on limited grounds and with detailed justification – though it must refuse authorisation if there is a negative ethics committee opinion. The Regulation also maintains the concept of tacit authorisation introduced by the Directive
- Risk-adapted regulations introduced to certain areas concerning the clinical trial master file, monitoring, deemed consent procedures and the traceability of investigational medicinal products (IMPs) for LICTs. For example, the extent and nature of monitoring determined necessary for a trial depends on its characteristics assessed by the sponsor. There are also reduced storage/return, authorisation, labelling and submission requirements for authorised IMPs and authorised auxiliary medicinal products – such as non-IMPs required by the protocol
- Under new rules introduced to promote transparency, the sponsor must notify concerned member states of the start, end, halt or termination of a clinical trial, and at the end of patient recruitment. Tight deadlines apply governing the submission of results and reports via the portal: a results summary must be submitted within one year from the end of the trial in all concerned member states, including a layperson summary. A clinical study report must also be posted within 30 days of completion of the marketing authorisation process, irrespective of success or failure
- More detailed rules on subject information and on informed consent, although these have not been fully harmonised and still allow concerned member states discretion in certain areas
- All safety reporting will be via a module of the EudraVigilance database operated by the EMA (2). Unless the protocol provides differently, an investigator must record and document all adverse events and report these to the sponsor, which, in turn, must report these to the EMA via the database. Deadlines for reporting depend on the nature and severity of the adverse event. Serious breaches of the Regulation or of the protocol will also become reportable – not just in the UK
- Co-sponsorship is expressly permitted. Although already recognised in some member states such as the UK, this is not currently the case in others, like Germany (3,4)

Overcoming Challenges

Timelines

One of the key hurdles for the industry will be meeting the tight deadlines for the sponsor to provide additional information requested by either the reporting or the concerned member states during the authorisation procedure. The sponsor only has

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a 10- or 12-day response period under the Regulation, including in cases where the requests concern individual site-specific information – such as the suitability of investigators or particular clinical trial sites. Timely responses are critical, as failure to respond within the prescribed deadline results in a deemed lapse of the application in all concerned member states, and a fresh application must be submitted. As a result, sponsors must be well prepared and able to quickly access expert local knowledge and mobilise relevant teams, including teams responsible for sites at a local level.

Authorisations and Refusals

Part one and two assessments ultimately lead to one of three outcomes: acceptance, acceptance subject to conditions, or refusal. Each concerned member state must notify the sponsor of its decision via the submission portal. However, appeals against member state decisions will be subject to national rules. This is likely to introduce additional uncertainty into sponsors' trial planning for multi-centre trials carried out in several member states. Sponsors will have to decide whether or not to proceed with certain sites, appeal or, instead, apply at a later date to extend the study to include those that were refused, on the basis of an adjusted application. This absence of a harmonised appeal procedure to manage refusals may discourage sponsors from initiating trials in more than one EU member state, contrary to the objective of the Regulation.

Legal Representative and Co-Sponsorship Liability

Ex-European Economic Area sponsors must establish at least a contact person in the EU (or in the member state concerned, if a study occurs in only one country). However, the Regulation also permits member states to require the legal representative to be responsible for ensuring compliance with the sponsor's obligations. As EU affiliates frequently act as legal representatives for parent company sponsors, they should clarify in advance what their direct potential liability exposure could be in relevant member states, and ensure that adequate intra-group controls, arrangements and, possibly, insurance are in place to protect them.

Furthermore, the Regulation expressly provides for co-sponsorship of clinical trials. Co-sponsors can allocate legal responsibility among themselves via a written contract, but must nominate a single sponsor with responsibility for compliance with procedural requirements, coordinating questions and responses from member states, investigators or subjects, and for implementing any corrective measures following a member state inspection.

If responsibility for a particular aspect of the trial is not specifically attributed to a co-sponsor, all co-sponsors will be deemed to have joint responsibility. It will therefore be vital that co-sponsorship agreements adequately address allocation of responsibility, and that such attributions are then reflected in outsourcing agreements – with sites, for example. Effective contract management and review processes will therefore be essential. Consequently, co-sponsors may choose to mitigate the risk of sub-standard or non-performance by applying appropriate due diligence on a prospective co-sponsor's capabilities and by obtaining appropriate insurance.

Ethics Committees

Some of the major concerns raised during the consultation process related to the role and nature of ethics committees and, in particular, the lack of a standardised quality accreditation mechanism for ensuring a uniform approach to ethical review. Many respondents requested the implementation of an accreditation system for ethics committees (5). One of the drafts of the Regulation stipulated that a clinical trial could be authorised in a member state despite disagreement of the relevant ethics committee. However, this scenario was heavily criticised by the German Medical Association and the German Parliament because, in Germany, a clinical trial must be approved by the corresponding ethics committee (6). As a result, the final Regulation maintains that mandatory national ethics committee approval is needed in order to carry out a clinical trial in a member state.

Clinical Data Transparency

By making trial data and information in the EU clinical trial database publicly accessible, the Regulation aims to achieve increased transparency which, according to the Regulation's recitals, "should contribute to protecting public health and fostering the innovation capacity of European medical research, while recognising the legitimate economic interests of sponsors".

Nonetheless, the mandatory publication of clinical trial data has caused industry concern. Pharmaceutical companies have commented that allowing non-experts free access to their raw data may mean it is misinterpreted, casting unnecessary doubt on the efficacy or safety of

products. Some believe that data may also be used by competitors in order to obtain their own regulatory authorisations or to acquire patents for new medicinal uses before the originating company is able to fully study the potential of their products. Controversy aside, the plan for improved transparency under the new Regulation reflects a broader tendency at the EU level to improve access to information and to narrow the scope of what is considered commercially confidential information (7).

Implementation of the Regulation will mean that sponsors have a legal obligation to file trial data, and access to this will be significantly less restrictive than has historically been the case. However, ahead of the Regulation, some companies have already responded to adverse publicity regarding alleged cover-ups in relation to the risks or efficacy of their products, by publishing clinical trial data on their own websites (8). The European Federation of Pharmaceutical Industries and Associations announced a similar plan for its members last year, while the EMA has also announced its final policy on the publication of trial data (9,10).

Preparing for Change

The new Regulation will introduce major changes to the administrative procedures governing the authorisation and conduct of clinical trials within the EU. From a practical perspective, the new regime is expected to fulfil the main objectives of lowering administrative burdens, streamlining processes and increasing transparency. At the same time, it poses significant challenges to the pharma industry.

Even though the Regulation will not come into force until at least 2016, companies would be well advised to start preparing early for the changes. This can be achieved by focusing on frontloading of preparation for trial authorisations and amendments; checking responsiveness of global and local teams (both internally and externally); ensuring completeness of clinical trial registration and data filing; and reviewing contractual templates and patient consent documentation, to confirm compliance, but also to guarantee potential liability exposure is adequately managed.

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