The hurdles of conducting clinical trials across different countries: focus on new European regulations

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Abstract
The new European Union (EU) regulation governing clinical trials and medicinal products became effective on June 16th, 2014 but full implementation is scheduled for May 2016 onwards. The repeal of the Clinical trial directive 2001/20/EC is welcomed because the old directive was a highly criticized piece of pharmaceutical-related legislation. The new legislation is binding and must be applied in all EU-28 member states, and will hopefully simplify and speed up clinical trial applications and authorizations. This article describes key innovations in the new legislation.

Key words: clinical trials, European Union, regulations

Introduction

The new European Union (EU) regulation governing clinical trials (CTs) and medicinal products became effective on June 16th, 2014 but are scheduled to be fully implemented from May 2016 [1]. This regulation will repeal the Clinical trial directive 2001/20/EC, one of the most criticized pieces of legislation in the pharmaceutical field. In fact, divergent national implementations of the previous directive resulted in delays starting trials, increased costs both for trial sponsors and authorities, and contributed to the approximately 25% decline in the number of CTs proposed and conducted in EU between 2007 and 2011 [2, 3]. Unlike the directive, the new regulation is a binding legislative act and must be applied in all the EU-28 member states. Some key changes will be introduced in order to simplify and speed up CT applications and authorizations. The innovations, described in detail below, include the creation of a central database and a review system coordinated by a reporting Member State (rMS), proposed by the sponsor, and the other Member States (MS).

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Main innovations

A new way for clinical trial application and authorization

As specified in Annex I and II, the sponsor will complete an application dossier about the initial evaluation and for subsequent substantial amendments. As reported in article 77, a single central portal used for all communications about the clinical trial will be created and maintained by the European Medicines Agency (EMA), who will set up also a unique European database (article 78; 81), available in all the EU languages. A single dossier for all European countries and a coordinated procedure will reduce paper work and requirement to know about all different national legislations and will facilitate information gathering. Moreover, all entered data will be available to both healthcare professionals and the public. The application dossier will include the curriculum vitae and financial disclosure statements for all investigators, and, if applicable, proof of damage compensation.
One of the major innovations is a coordinated assessment procedure which is divided into two parts, running in parallel: Part I is general for all European countries and Part II is specific for each nation. The rMS is the responsible for risk-benefit assessment, coordinates all the procedures and creates draft reports in agreement with other MS; meanwhile all MS individually evaluate ethical and local regulations, including informed consent. The rMS decision about core topics of the application will be available at the same time for all MS. Such procedure facilitates real cooperation in the assessment phase and permits the sharing of expertise and considerations

between MS. Even if the conclusions of the rMS would usually be accepted by other MS, there is the possibility of "qualified opt-out" for each MS if there are important differences between usual clinical practice and practice chosen by the rMS or if the decision on Part I conflicts with national legislation [4]. In order to reduce the assessment time for authorizations, which has been reported to be between 140 and 301 days [5], the new regulation defines specific timelines, both for the initial application (minimum 60, maximum 106 days) and for substantial amendments (minimum 49, maximum 95 days). If a MS fails to communicate its decision about Part I within the defined timelines, the rMS' evaluation is considered to have been accepted (tacit approval maintained).

Both Parts I and II create one single decision issued by a MS. Where applicable, there is one fee for each MS, which can be reduced for academic sponsors. These innovations mean that the start date for clinical trials can be scheduled across all European countries within a defined period, and could also facilitate planning of costs for assessment procedures.

Application of this regulation is not possible until May 2016, when the EU-Portal and EU-Database will be activated. Therefore, there will be a transition period for the MS, during which they can be informed about the new requirements, implement new procedures and documentation, and train staff involved in clinical trials.

Damage compensation

Each MS must ensure that systems for compensation for any damage suffered by subjects as a result of participating in low intervention CTs (see below) are in place, such as liability insurances, guarantees or similar solutions. Both the sponsor and investigator shall make use of the system, which should be appropriate for the nature and the extent of risk. There is no requirement for additional use of the system for low-intervention CTs where the possible risks resulting from use of the investigational medical product (IMP) are covered by applicable compensation systems already in place. Although this provides a new framework for damage compensation, there is the risk of discrepancies and no harmonization between countries in Europe because the responsibilities described above are applicable to a single MS.

The "co-sponsorship"

The new regulation introduce the concept of "co-sponsorship". A clinical trial can have one or more sponsors, facilitating academic CTs conducted in different MS or with trial sites outside Europe. In this situation, responsibilities will be split between the different sponsors, as described in a written contract. There are still some points that need to be addressed with this, such as the definition of a sponsor for compliance with authorization procedures, the contact point for questions and responses, and the methods of implementation. In addition, it is unclear how the responsibility will be split (e.g. on the basis of sponsoring entity or in accordance with area of competence).

The sponsor and the investigator can be the same entity (article 68). The sponsor can delegate the role of investigator to another subject, with a written contract, but retains overall responsibility for the clinical trial.

The risk-based approach: low-intervention clinical trials

Article 2 provides the definition for low-intervention CTs, which are trials conducted with authorized IMPs (excluded placebos) that have a defined set of features: IMPs are used in accordance with the terms of the marketing authorization (MA) or their use is evidence-based and supported by published scientific evidence of efficacy and safety in any of the MS, with minimal additional risk or burden for diagnostic and monitoring procedures compared with normal clinical practice in any MS. For these reasons, low-intervention CTs require less stringent regulations for monitoring, documentation, damage compensation (see above), drug labelling and accountability.

The recognition that there are differences between CTs in the risk involved is aligned with the recommendation of the Organization for Economic Cooperation and Development (OECD) of 10 December 2012.

The future reporting requirements

Reporting requirement procedures will be simplified. A sponsor will communicate to the EMA through the EU-Portal and the EMA will directly inform all MS. In addition, the number of reported events could be reduced because the approved protocol can declare that not all the adverse events (AEs) are to be recorded by the investigator. There will be no report of unexpected serious adverse reactions (SUSARs) to Ethics Committees (ECs) and the responsible EC of each MS can be involved in the SUSARs assessment and annual reports, only if it is expected by a specific national law. In order to reduce the burden of reporting, there is the possibility of creating one single annual report to be submitted for different IMPs used in the same clinical trial.

The EU-Portal will be the single source for safety reports all over Europe; nonetheless there is the possibility of re-

porting directly to the national competent authorities (CA) if the electronic reporting is not available to a sponsor.
These changes mean that the major focus in the future will be on relevant reports, even though the EU-portal will allow minor reports to be highlighted as well.

Transparency

The EU-Database will allow reporting of not only inspection reports, information applications, timelines and notifications about trials status, but also the study results, including a report summary and a lay summary one year after the end of the trial. Sharing of raw data will be on voluntary basis [6].
The sharing of information could reduce duplication of CTs and make cross-referencing easier, which will be particularly helpful during the design of trials. The creation of a single database will make it easier for investigators, sponsors and the public to gather information.

Subject safety

The new regulation provides the opportunity to conduct CTs in emergency settings, where subjects cannot immediately provide consent and permits the use of deferred consent under clearly specified conditions. This may promote research in emergency settings that assesses interventions with a minimal risk compared to standard practice [7].
The trials will have a broad consent about use of data, which will allow future research on topics not yet known to the investigators, if national legislation permits. Subjects can withdraw consent at any time, but, in contrast to the previous directive, withdrawal of consent does not affect use of data obtained before that withdrawal. It is expected that this will improve the quality of data and the resulting reliability of trials.

Potential pitfalls and future challenges

There is no doubt that the new regulation represents a huge step forward for the conduct of CTs in Europe, but there are also some potential problems in its application. Firstly, full functionality of the EU-Portal and Database are critical for operation of the entire system, but set up might take a long time, with resulting delays in achieving the possible benefits of this regulation. Secondly, the strict timelines described above could prevent or delay important CTs if response times for requests are missed by the sponsors.
It is also important to note the clarified role of ECs in assessment procedures. ECs are independent bodies in a MS that have been empowered to give opinions that take different standpoints into account, particularly those of patients or patients' organizations. If an EC is involved in assessment phases, it will need to adhere to the defined timelines. To improve cooperation between the ECs of different MS, it might be necessary to increase the frequency of EC meetings or to create a national EC. There are procedures in place to monitor the impact of the regulation every 5 years and this could be a useful process by which to introduce enhancements. Moreover, in the future, it is important to consider an increase in patients' involvement, which is significantly reduced compared with proposals by the EU commission.

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