



Main changes in European Clinical Trials Regulation (No 536/2014)

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ABSTRACT

The new Regulation (EU) No. 536/2014 for clinical trials of medicinal products for human is part of a European regulatory framework in which the European Commission has wished to give a strong impetus to scientific research and industrial progress. It is a new regulation that fills a series of regulatory gaps in the Clinical Trials through the creation of a uniform framework for the authorization of clinical trials by all interested Member States with a single assessment of the results. The Regulation thus facilitates cross-border cooperation to make the clinical tests wider and encourage the development of special treatments, for example for rare diseases, but above all streamlines the rules on clinical trials across European Union (EU), introducing simplified rules for experimentation so-called 'low level of intervention', on which much has been discussed and still arouses concern, providing for authorized medicines or used off-label in the presence of scientific evidence published on efficacy and safety and to benefit from they will be mainly the pediatric and oncological therapeutic areas. The applications and any communication will be submitted paperlessly via a new electronic EU portal. The complex processing procedures and shorter time limits are to be stressed in comparison to the previously valid regulations. This is a major challenge for all stakeholders, but on the other hand it should contribute to the future role of the EU in the development of innovative medicines.

1. Introduction

The number of applications for authorization to clinical trials in EU decreased by 25% between 2007 and 2011; the clinical costs of conducting clinical trials increased and the average waiting time for clinical trials increased by 90%–152 days [1]. The current provisions of Directive 2001/20/EC seem to have hindered the conduct of clinical trials in EU. On 17 July 2012, for the first time, the European Commission proposed a new Regulation on Clinical Trials for Medicines because it considered that a Regulation was the best tool to promote robust data generation and in line with the requirements of medication research, at this time of globalization and potential loss of Europe's attractiveness for clinical trials, which are at the same time an opportunity for economic development and early access to innovative medicines while ensuring maximum patient protection in respect for the principles of ethics and the safeguarding of individual rights. Following a complicated and sometimes controversial process of negotiation, the Regulation was adopted in April 2014 by the European Parliament and published on 27 May 2014 in the Official Journal (OJ) and applied since 2017 [2].

1.1. Purpose of regulation

The objective of the new European Regulation applicable in all Member States is the almost complete harmonization of the approval process for clinical trials and the introduction of a common evaluation for multinational clinical trials; the choice of a Regulation rather than a Directive for the harmonization of rules on clinical trials in the various Member States, minimizing the scope for regulatory autonomy at national level, making Europe competitive in research (considering the decline in clinical trials and number of patients in the last few years), ensuring the production of reliable and robust, high-level scientific data, ensuring patient safety [3].

The general aspects of harmonization include: a harmonized authorization dossier, a single portal managed by the European Commission, to submit an application for authorization to conduct a clinical trial linked to a European database; a rapid evaluation procedure involving all the Member States where the sponsor intends to conduct the trial; precise time limits. The date of the first application of the Regulation is scheduled for September 2018; Directive 2001/20/EC remains valid for a maximum of 3 years after the date of application of the Regulation. There will be a transition period for the old and the new procedures, so that both procedures will be in parallel for a maximum

Abbreviations: EU, European Union; EC, European Commission; MA, Marketing authorization; CI, Informed Consent; MS, member states; rMS, reporting member state

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of 3 years. An application for approval may be submitted one year after its entry into force, in accordance with the old or the new legislation [4].

1.2. Key changes

In order to outline terminology, the regulation defines the term “clinical trial” as a study designed to:

- (a) to investigate or confirm the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products;
- (b) to detect any side effects of one or more drugs or
- (c) study the absorption, distribution, metabolism or excretion of one or more medicinal products, in order to establish the safety and/or efficacy of these medicinal products.

A clinical trial may be a clinical trial or a non-interventional study. It is considered a clinical trial if it meets at least one of the following additional criteria:

- (a) the candidate will be assigned in advance to a specific treatment strategy that does not correspond to the normal clinical practice of the Member State concerned;
- (b) the decision to prescribe the experimental medicinal product is taken together with the decision to include the subject in the clinical trial or
- (c) patients are undergoing diagnostic or monitoring procedures that go beyond normal clinical practice.

If a clinical study does not meet any of the above criteria, it is considered a non-interventional study to which the regulation does not apply. Contrary to the definition of Directive 2001/20/EC, the definition of a non-interventional study will therefore not have any relationship with the status of drug approval in the future.

With the new regulation, the new concept of low - level clinical trials will be introduced: the experimental drug is authorized and used in accordance with the Marketing Authorization (AIC) or on the basis of scientific evidence. This type of experimentation has diagnostic or monitoring procedures with minimal risk or additional burdens for the safety of subjects compared with normal clinical practice. For this type of experimentation, no ad hoc assurance is provided and simplified acquisition of informed consent by the designation of groups of subjects rather than isolated subjects is allowed. The proposal for regulation notes that clinical trials do not always have an additional risk for subjects compared to treatment in normal clinical practice. Consequently, in the absence of additional risks, or if such risks are negligible, there is no need to provide specific compensation (in the form of insurance or compensation) for clinical trials. In such cases, the insurance coverage of the doctor, the institution or the liability insurance product offers sufficient coverage.

Protecting subjects and getting informed about informed consent (IC). The new regulation provides for the possibility of requesting a Broad Consensus (BROAD) for further future analysis, which the patient can at any time revoke. A simplified ICI for CLUSTER TRIALS: trials comparing standard (authorized) treatments, and where randomization is not for patient but for Clinical Center, will be admitted.

The new Regulation does not substantially change the rules on the protection of individuals and informed consent introduced by Directive 2001/20/EC; some provisions are reformulated and/or synthesized to facilitate their understanding. Exception is the New Standard on Clinical trials in Emergency Situations: Unlike Directive 2001/20/EC, the new Regulation specifically regulates cases where, due to the urgency conditions, it is not possible to obtain free and informed consent beforehand.

1.3. Authorization procedures

Close cooperation between the Member States (MS) has been introduced, with a single submission of the application for experimentation in all States in which it will be conducted and a joint assessment by all National Authorities, guided by a Member State will act as Rapporteur. Clinical trials will also be divided into traditional and low - level interventions, and can be evaluated in separate phases for the scientific and ethical parts. There is also a significant increase in transparency on clinical trial data and data generated, with a greater involvement of the public and patients, with the mandatory introduction of a patient into the testing team and the publication of a final report in language dedicated to the public and not to the workforce.

The evaluation procedure will include a reporting Member State (rMS), a rapporteur Member State that coordinates Evaluation and Concerned Member State (s). The procedure will be divided into 3 steps: validation, evaluation, decision.

The evaluation report will be divided into two sections, a science and ethics, which can be presented at the same time or in separate phases; the final decision will be, however, unique for each Member State.

Part I = > on technical, scientific, non-clinical and clinical quality. State of knowledge, clinical question, hypothesis to be tested, clinical relevance, goals, endpoints, safety measures, risk/benefit.

Part II = > ethical aspects and local feasibility (patient information/informed consent, letter to the treating physician, how to enroll, insurance, PI fitness and clinical center, any refunds.)

The Rules leave SMs free choice on the involvement of the Ethics Committees (EC) in the evaluation process (while respecting the established times).

However, it has been reaffirmed that the Commission expects from the Ethics Committees an assessment of “local feasibility”, as the authorization is expressed centrally.

If an SM intends to involve the Ethics Committee for ethical and scientific evaluations (ethics and science are inseparable), and you do not see how it can be avoided, the ethics committee will also have to interact with the Single Portal. If involved, ethical committees should have at least weekly meetings frequencies. In order to obtain additional information from the Sponsor, the rapporteur Member State (rMS) may extend the deadline of a further 31 days. For the purposes of expert consultation, the rapporteur may extend the term of 45 days of additional 50 days for clinical trials involving the use of advanced therapy medicinal products.

1.4. Sponsor and examiner

The decree confirms sponsor and examiner terms with respect to the previous settlement and redefines the term of the main auditor. A sponsor is “a person, entity, organization that assumes the responsibility to initiate, manage and fund clinical trials.” The direct link to funding, which was still included in the directive, will no longer be applicable in the future. New is the definition of the main auditor. This is the head of a group of examiners conducting clinical trials at a center. Examiners are defined as persons responsible for conducting clinical trials at a center. As before, this task is not restricted to doctors alone, however, pharmacological treatments can only be performed by doctors.

1.5. New rules on security communications

Compared with Directive 2001/20/EC, these standards have been streamlined, simplified: there is an option for the experimenter not to notify the sponsor of adverse events if this is provided in the protocol; there is a direct disclosure of suspicious suspected adverse negative side

effects by the sponsor to the European Eudravigilance database and a simplified presentation of the sponsor's annual security report. In addition, the annual safety report is not presented for authorized medicinal products that are used within the limits of their authorized indication [5].

1.6. EU portal an data bank

The EU portal is a key application as a hub for all communications on clinical trials in Europe. EU portal is established and maintained by the agency, it will adsorb the EudraCT. Is the access point for a single application dossier from part of the sponsor to the Member States. Data and information acquired through the portal they will have to be inserted in one European Data bank. There will be a single EU number for each clinical trial, an EU number for each medicine without AIC, information in an easy-to-consult format, an interface for users in all EU languages. The Data Base will be continuously updated and accessible to the public unless some or all of the data and information contained therein justify its confidentiality.

2. Discussion

The new EU regulation is very detailed and structured in a comprehensive way. The approval processes described in the Regulation mainly concern multinational procedures. In the future, the rapid processing of approval processes and communication obligations through the EU portal will give relief to sponsors, national authorities and ethics committees. Evaluation of the application documents for Part I of the Evaluation Report will in the future be largely done jointly by the Ethics Committees. Short processing deadlines and the complex assessment procedure require, on the one hand, a high level of human resources and, on the other hand, a high level of technical competence and represent a major challenge for all concerned Member States. The new rules will have to ensure that the EU remains an attractive attraction for clinical research - which is vitally important for Europe's competitiveness and capacity for innovation. The fact that the new rules have been

included under a Regulation and not a Directive makes them directly applicable throughout the European Union. The scope of the proposal for a Regulation is essentially identical to that of Directive 2001/20/EC. The scope of application is limited to clinical research on medicines, but is very wide, as it excludes only clinical trials that do not involve “intervention” (eg doctors' investigations without further intervention or data mining).

3. Conclusions

Directive 2001/20/EC had introduced significant improvements in the safety and ethical validity of clinical trials in the EU and in the reliability of data obtained from clinical trials, but has been severely criticized in the pharmaceuticals sector.

The new regulation introduces some important measures that should contribute to increasing clinical research in Europe.

Acknowledgements

None.

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