

Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use: an overview

Carlo Petrini

Unità di Bioetica, Presidenza, Istituto Superiore di Sanità, Rome, Italy

Abstract

For the 28 member states of the European Union, Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use, which repeals Directive 2001/20/EC, represents a substantial innovation in the procedures for authorising clinical trials and for handling all the subsequent stages. It introduces a single authorisation that will be valid for all EU member states, as well as a single portal through which all data concerning all clinical trials performed throughout the EU will pass. The present article offers an overview of the general aspects of the new procedures. It does not address the specific issues involved, each of which merits separate examination.

Key words

- Europe
- human experimentation
- legislation

INTRODUCTION

Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16th April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC [1], establishes a new set of harmonised rules that all member states are required to apply in all clinical trials performed throughout the European Union (EU).

The Regulation is long and detailed (99 articles, divided into 19 chapters, plus 7 annexes) and, as it is a Regulation rather than a Directive, is immediately applicable and binding in all member states, without the need for it to be transposed into the legislation of individual states. Regulations are thus of particular importance.

The Regulation aims, among other things: to ensure that the procedures for authorisation are efficient and rapid; to simplify specific sponsor obligations; to guarantee public access to information regarding clinical trials. To this end the European Medicines Agency (EMA) will cooperate with member states to set up and maintain a portal and database at Union level.

The present article describes those parts of the Regulation that, in general, affect the path of a request for authorisation, from submission to assessment and the final decision. Given the complexity of the procedure, it offers an overview of the Regulation and does not discuss specific sections that concern such issues as: notification of the start, conclusion or temporary halt of a clinical trial and of the end of the recruitment of subjects; substantial modifications to the protocol;

the labelling of investigational medicinal products and auxiliary medicinal products; safety reporting (adverse events and unexpected serious adverse reactions); the protection of specific categories of subjects; compensation for damages; supervision by member states, inspections and controls at EU level; specific rules for specific circumstances, such as cluster trials or clinical trials in emergency situations.

OVERVIEW

The need for a review of the regulatory framework for clinical trials was widely recognised in view of the problems raised by Directive 2001/20/EC [2], particularly in regard to: differences in implementation levels across member states; the excessive levels of bureaucracy involved in meeting the administrative requirements of the Directive, some of which were not effectively justified; the need for multiple applications for trials involving more than one state; difficulties in handling divergent decisions, especially in relation to the opinions expressed by ethics committees; the lengthy and uncertain time intervals required for authorisations; and the shortcomings of the Directive with regard to the increasingly global scale of clinical trials [3, 4]. The debate on how to move beyond the Directive involved numerous parties [5] and lasted several years [6] before culminating in the adoption of the Regulation.

The Regulation entered into force on 16th June 2014 but will not be applicable until six months after the EU portal and database have become fully functional, and in any case not before 28th May 2016.

An interim period of three years is envisaged, during which trials for which a request for authorisation was submitted before the entry into force of the Regulation will continue to be governed by Directive 2001/20/EC. A period in which the two systems will overlap is also envisaged, with the effect that submissions under the current system will be valid until at least 28th May 2016.

In agreement with principles widely shared throughout the world [7] and stated in earlier documents concerning clinical trials [8], one of the key general principles established in the Regulation is that a clinical trial may be performed only if “the rights, safety, dignity and well-being of subjects” are protected and the data generated are “reliable and robust”. In addition, the “interests of the subjects should always take priority over all other interests”.

SCOPE AND DEFINITIONS

The Regulation applies to all clinical trials conducted within the EU. A long list of definitions (Article 2) distinguishes between “clinical studies” and “clinical trials”. Because the two definitions are particularly important to understanding the scope of the Regulation, it is worthwhile quoting them in full:

- “*Clinical study* means any investigation in relation to humans intended: a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products; b) to identify any adverse reactions to one or more medicinal products; or c) to study the absorption, distribution, metabolism and excretion of one or more medicinal products; with the objective of ascertaining the safety and/or efficacy of those medicinal products”.

- “*Clinical trial* means a clinical study which fulfils any of the following conditions: a) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned; b) the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study; or c) diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects”.

Thus only interventional studies are “clinical trials” and fall within the scope of the Regulation: the Regulation does not apply either to non-interventional studies or to medical devices (unless they are part of a clinical trial involving a medicinal product).

The Regulation also defines new concepts absent from the earlier rules.

These include:

- *Low-intervention clinical trials*: these are trials that use authorised (rather than investigational) medicinal products and that do not pose a substantial additional risk compared with clinical practice. The procedures for these categories of trial are simpler and involve fewer obligations regarding monitoring, traceability and insurance;

- *Co-sponsor*. The sponsor, a figure already present in the earlier regulations, is the health centre (or person) responsible for a clinical trial. Because the or-

ganisation of trials frequently entails the intervention of several organisations rather than a single party, the Regulation envisages the possibility of “co-sponsors” who share the same responsibilities unless a different arrangement is set out in a written contract;

- *Auxiliary medicinal products*. These are products included in the protocol of a clinical trial but not as investigational products.

One particularly important issue addressed is the public disclosure of clinical trial data. The EU database will contain a summary of the results of trials as well as a summary for laypersons, which the sponsor is required to submit within a year of the conclusion of the trial (regardless of the outcome): the clinical study report must be submitted within 30 days of obtaining marketing authorisation or withdrawing the application. All the information on the EU database will be accessible to the public, with the exception of: personal data; confidential commercial information (unless there is an overriding public interest in disclosure); confidential communications between Member States relating to the assessment report; information whose disclosure would jeopardise effective supervision of the conduct of a trial by Member States.

AUTHORISATION PROCEDURE FOR CLINICAL TRIALS

The Regulation prescribes a precise and detailed procedure for the submission, assessment and evaluation of requests for authorisation of clinical trials.

This section briefly examines the key stages of this procedure.

The Regulation requires that the application dossier for clinical trials comprises two parts.

Part I – which deals mainly with the type of clinical trial, risk-benefit analysis, compliance with technical requirements – is assessed by the so-called “reporting member state” chosen by the sponsor of the trial from the 28 EU member states. The Part I assessment submitted by the reporting member state is valid for the entire EU. According to the regulations in force prior to approval of Regulation 536, specific authorisation for multi-centre trials to be conducted in different states had to be obtained in each participating state. For trials performed in all 28 member states it was thus necessary to submit 28 dossiers to as many regulatory authorities and to apply for 28 authorisations. Regulation 536 provides instead for a single application and a single authorisation, and is expected to simplify and streamline considerably the process of obtaining authorisation.

Part II deals with intrinsically national aspects, such as informed consent and the compensation of subjects, which are assessed by each state separately in a procedure that also involves ethical committees.

As the procedures for assessment and decision-making are different for Parts I and II it is worthwhile examining them separately.

Part I

The sponsor proposes a reporting member state, which performs the assessment in cooperation with

the other member states concerned. The proposed reporting member state may refuse to be the reporting member state, or another member state may propose to be the reporting member state within three days of submission of the application dossier.

Annex I of the Regulation lists the items that must be contained in Part I of the dossier (common to all the member states concerned), including, among others: introduction (covering, where appropriate, previous applications, co-sponsors, etc.); cover letter; application form; clinical trial protocol; investigator's brochure; documentation relating to compliance with Good Manufacturing Practice (GMP); Investigational Medicinal Product Dossier (IMPD); Auxiliary Medicinal Product Dossier; copy or summary of any scientific advice of the European Medicines Agency and Paediatric Investigation Plan (PIP), where appropriate; content of the labelling of the investigational medicinal products; proof that data will be processed in compliance with Union law on data protection.

The Regulation states that "it should be left to member states to establish the language requirements for the application dossier", but the recommendation that "a commonly understood language in the medical field" be used seems an implicit suggestion that English is the preferred language. The possibility of submitting applications in languages other than English will have to be tested in practice.

Applicants may refer to data generated by another clinical trial only if the other trial was conducted either in compliance with the Regulation or, in the event it was performed prior to full application of the Regulation, in compliance with Directive 2001/20/EC.

If the clinical trial referred to was conducted outside the Union, it must have been conducted "in accordance with principles equivalent to those of the Regulation as regards the rights and safety of the subject and the reliability and robustness of the data generated". Data generated in clinical trials initiated prior to full application of the Regulation are to be submitted in an application dossier only if the trial was registered prior to its start in a public register that is a primary or partner registry of, or data provider to, the World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP), or if its results were published in an independent peer-reviewed scientific publication.

The Regulation establishes brief and precise timelines.

Applications are to be validated within 10 days of their submission by the sponsor, and the reporting member states (for Part I of the dossier) and the member states concerned (for Part II of the dossier) must submit an assessment report within 45 days of the validation date. As already noted, only one validation of Part I – which is valid throughout the EU – is required for each trial.

In the event that supplementary information is required, a single extension period is granted, totalling not more than 15 days (10 days for the sponsor to respond and 5 days for the decision by the reporting member state).

An additional extension of 50 days is possible for

clinical trials that involve particular types of medicinal products, specifically advanced therapy investigational medicinal products.

A system of tacit approval is established in the event a member state does not respond within the period specified.

Parts I and II may be submitted together, or Part I may be submitted in advance for review and agreement before the submission of Part II. In addition, if the sponsor so requests, "the application for authorisation of a clinical trial, its assessment and the conclusion shall be limited to the aspects covered by Part I of the assessment report". Following notification of the conclusion regarding the aspects covered in Part I, the sponsor may, within two years, apply for "an authorisation limited to aspects covered by Part II of the assessment report", in which case he must declare "that he is not aware of any new substantial scientific information that would change the validity of any item submitted in the application" regarding aspects covered by Part I. If Parts I and II are submitted separately, Part II may not be presented before the assessment of Part I has been completed.

The separate submission of Part I before that of Part II could be useful in cases involving particularly complex protocols whose design and acceptability need to be agreed before additional details can be defined to take account of local peculiarities.

During the initial assessment of Part I, the reporting member state prepares a draft assessment report that is circulated among the member states concerned for their consideration and comments. The reporting member state then sends the final scientific assessment report to the sponsor within 45 days of validation of the submission. During this period the reporting member state (but not the member states concerned) may ask the sponsor for additional information, in which case the deadline for the response is extended by 31 days (for a total of 76 days), made up as follows: 12 days for the sponsor to reply; 12 days for a coordinated review, 7 days for the reporting member state to finalise the assessment report, which will declare that the trial is: acceptable; acceptable subject to conditions; or not acceptable. The deadlines are calculated on the basis of calendar days, not working days.

Part II

Part II contains country-specific information: recruitment arrangements; subject information; informed consent form and informed consent procedure; suitability of the investigator; suitability of the facilities; proof of insurance cover or indemnification; financial and other arrangements; proof of payment of the fee.

Part II is assessed separately in each member state concerned and covers: informed consent; rewards or compensations; arrangements for recruitment; compliance with Directive 95/46 (data protection) [9]; suitability of the sponsor or of the Contract Research Organisation (CRO) to conduct the clinical trial; adequacy of the insurance; compliance with provisions

on the collection, storage and use of biological material. These aspects are examined by ethics committees.

If Parts I and II are submitted together, the deadline for notification of the final decision on Part II is the same as that for Part I, *i.e.* 45 days after validation of the submission. Each member state may, “with justified reasons”, asks the sponsor for additional information, limited to the aspects covered in Part II. In this case the deadline for the decision may be extended by 31 days (12 of which are for the sponsor to reply and 19 for the member state to finalise the decision). If the assessment of Part I takes up the full period of 76 days the decision must be given within five days thereafter.

If a member state concerned fails to communicate its decision within 5 days of the reporting date of the assessment of Part I or of the end of the assessment of Part II (whichever is later), the decision given in the final assessment of the reporting member state shall be deemed to be valid.

A member state that does not accept the decision on Part I of the assessment report shall not participate in the trial.

A member state may reject the decision on Part I in the following circumstances:

- if it considers that participation in the clinical trial would lead to a subject receiving treatment inferior to that which he or she would receive in normal clinical practice in the member state concerned;
- if the clinical trial involves a violation of specific “national law prohibiting or restricting the use of any specific type of human or animal cells, or the sale, supply or use of medicinal products containing, consisting of or derived from those cells, or of medicinal products used as abortifacients or of medicinal products containing narcotic substances within the meaning of the relevant international conventions in force”;
- on grounds of considerations regarding data reliability and robustness raised by the member state concerned during the assessment of Part I.

GENERAL COMMENTS

The Regulation introduces procedures with very precise timelines. The requirement of a single submission and a single approval for Part I that are valid throughout the EU will considerably simplify the authorisation process.

Some of the operational aspects regarding the submission, assessment and decision still have to be defined, presumably when the Regulation becomes fully applicable.

On the basis of the above, it is worth indicating the following:

- The designation of a single reporting member state whose assessment and decision are valid throughout all 28 EU member states could, for various reasons, lead to sponsors giving preference to some states over others. It is therefore to be expected that a limited number of states will act as reporting member state for the majority of trials.

- Compliance with the deadlines indicated in the Regulation will involve a considerable effort and may cause a number of operational problems both for the competent authorities and for ethics committees.

- Coordination between competent authorities and ethics committees will need to be carefully established, particularly when Parts I and II are presented together and the two assessments are processed in parallel within the same national timetable.

- The Regulation does not fully clarify some of the operational aspects concerning the role of ethics committees in assessing Part II. Specifically, it is not clear whether the issue of an opinion by an ethics committee is part of Part II: the data sent through the EU portal do not appear to include approval of ethical aspects, although those relating to Part II, which specifically concerns ethical aspects, are included. Nor does the Regulation clarify whether approval is required by each local ethics committee or only at national level. It is probable that local ethics committees will consider issues affecting local sites and that a single decision on the trial will apply per country.

- The requirement that data concerning trials and a summary of the results be made accessible to the public, including laypersons, is in agreement with a widely practised approach [10]; a similar position is included in the most recent revision of the Declaration of Helsinki [11], which includes two articles devoted specifically to “Research Registration and Publication and Dissemination of Results”. Article 35 states that: “Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject”. Article 36 states that: “Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication (...)”. The EMA has on several occasions been urged to review its policies on the publication of and access to clinical trial data [12] and is looking into the issue [13]. However, not all the rules for access to data have yet been wholly clarified. It would be reasonable, for instance, to ensure the confidentiality of trial results until marketing authorisation is granted.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

Received on 3 September 2014.

Accepted on 14 October 2014.

REFERENCES

1. European Parliament, Council of the European Union. Regulation (EU) 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. *Official Journal of the European Union* 27 May 2014;L158:1-76.
2. European Parliament and Council of the European Union. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. *Official Journal of the European Union* 2001;L121:34-4.
3. Editorial. Clinical research in Europe-trials and tribulations. *Lancet* 2012;379(9828):1764. DOI: 10.1016/S0140-6736(12)60742-9
4. Kenter MJH, Cohen AF. Re-engineering the European Union Clinical Trials Directive. *Lancet* 2012;379(9828):1765-7. DOI: 10.1016/S0140-6736(12)60430-9
5. Cancer Research UK, Academy of Medical Sciences, Association of Medical Research Charities - AMRC, Arthritis Research UK, British Heart Foundation, Medical Research Council - United Kingdom *et al.* Revision of the EU Clinical Trials Directive. *A joint statement from non-commercial research organisations in the UK*. 2011. Available from: www.acmedsci.ac.uk/download.php?file=/images/project/Jointsta.pdf.
6. European Parliament, Council of the European Union. *Proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC*. COM/2012/0369 final. 2012/0192 (COD). 12 July 2012. Available from: <http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52012PC0369>.
7. Jonsen AR, Veatch RM, LeRoy W. *Source book in bioethics. A documentary history*. Washington DC: Georgetown University Press; 1998.
8. Council of Europe. *Convention for the Protection of Human Rights and Dignity of Human Being with Regards to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine*. 4 April 1997. Available from: <http://conventions.coe.int/treaty/en/treaties/html/164.htm>.
9. European Parliament, Council of the European Union. Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data. *Official Journal of the European Communities* 23 November 1995;L281:31-50.
10. Chalmers I, Glasziou P, Godlee F. All trials must be registered and the results published. *BMJ* 2013;346:f105. DOI: 10.1136/bmj.f105.
11. World Medical Association. *Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects*. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975; 35th WMA General Assembly, Venice, Italy, October 1983; 41st WMA General Assembly, Hong Kong, September 1989; 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996; 52nd WMA General Assembly, Edinburgh, Scotland, October 2000; 53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added); 55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added); 59th WMA General Assembly, Seoul, Republic of Korea, October 2008; 64th WMA General Assembly, Fortaleza, Brazil, October 2013. Available from: <http://www.wma.net/en/30publications/10policies/b3/>.
12. Goldacre B, Godlee F, Heneghan C, Tovey D, Lehman R, Chalmers, Barbour V, Tracey B. Open letter: European Medicines Agency should remove barriers to access clinical trial data. *BMJ* 2014;348:g3768. DOI: 10.1136/bmj.g3768.
13. European Medicines Agency. *Publication and access to clinical-trial data*. EMA/240810/2013. Draft. 24 June 2013. Available from: www.ema.europa.eu/docs/en_GB/document_library/Other/2013/06/WC500144730.pdf.