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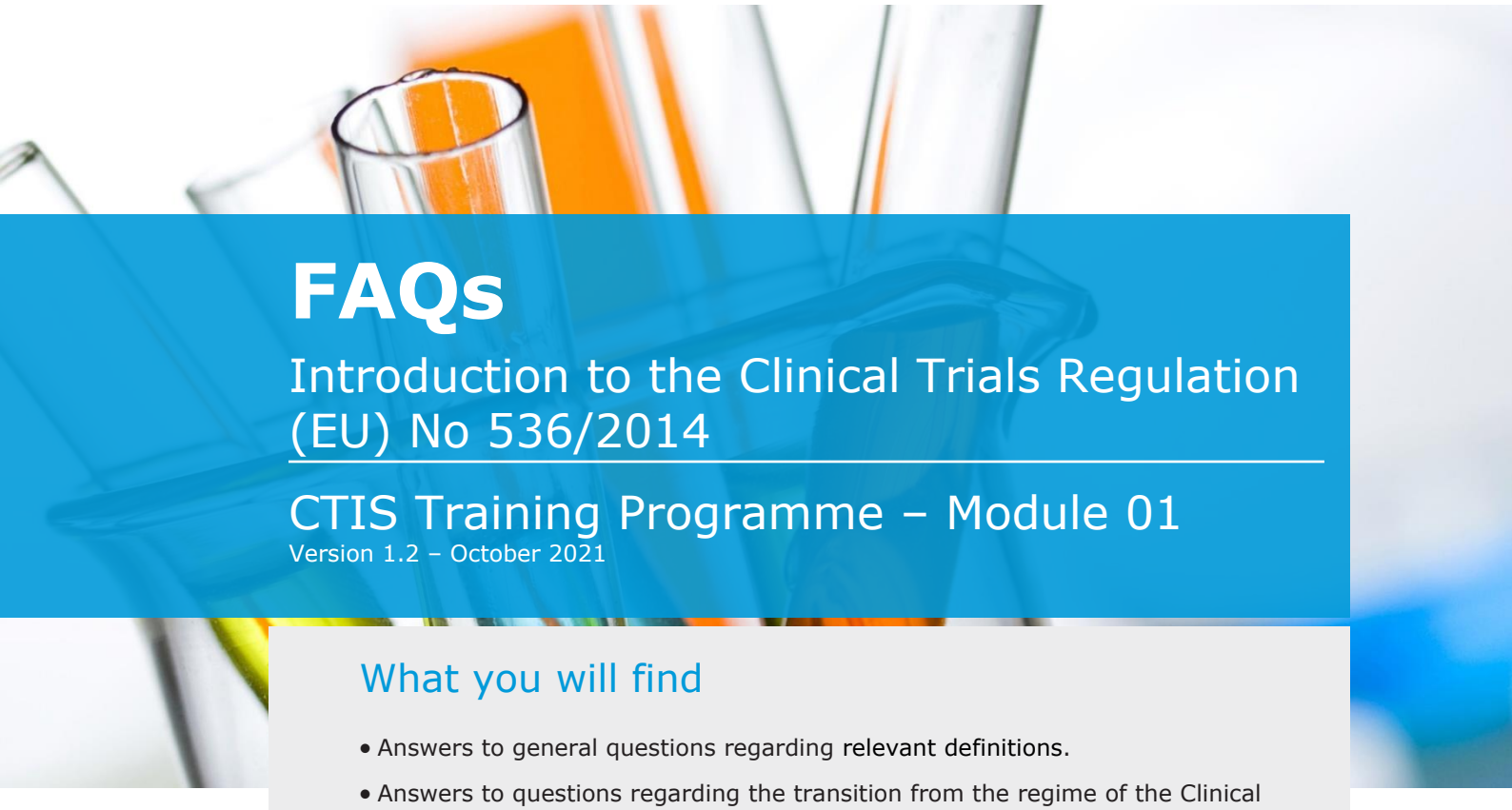

FAQs

Introduction to the Clinical Trials Regulation (EU) No 536/2014

CTIS Training Programme – Module 01

Version 1.2 – October 2021

What you will find

- Answers to general questions regarding relevant definitions.
- Answers to questions regarding the transition from the regime of the Clinical Trials Directive to the Clinical Trials Regulation.
- Answers to questions regarding the rules of transparency of clinical trials data, established in the Clinical Trials Regulation.

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FAQs

In this document, we list common questions regarding *Module 1: Introduction to the Clinical Trials Regulation (EU) No 536/2014*. They are categorised into three subsections focusing on definitions, the transition from the regime of Directive 2001/20/EC (Clinical Trials Directive) to the Clinical Trials Regulation, as well as the rules of transparency of clinical trials data, established in the Clinical Trials Regulation. This document has been prepared taking into account the Clinical Trials Regulation[1] itself and the European Commission's Questions & Answers Draft document on the Clinical Trials Regulation[2]. The specific learning objectives of this module are:

1. Understand the scope and objectives of the CT Regulation.
2. Understand the key changes of the CT Regulation compared to the CT Directive.
3. Understand the transition period from the CT Directive to the CT Regulation.
4. Remember the actors targeted by the CT Regulation and its benefits for each of them.

We encourage you to read these questions and answers carefully. If you have any questions that are not covered in this document, please contact us at CT.Training@ema.europa.eu so that we can update this document accordingly. This document will be progressively enriched with the input of the experts involved in the validation of the training material, the Master Trainers disseminating the materials, and the end-users.

[1] Regulation (EU) No 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use, *EU Official Journal* L158. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf

[2] European Commission, *Clinical Trials Regulation (EU) No 536/2014 Draft Questions & Answers*, version 4, July 2021. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf

1. Definitions

1.1. What is a 'clinical trial'?

According to article 2(2) (1 and 2) of the Clinical Trials Regulation, a clinical trial is 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 the 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."

1.2. What is a 'clinical study'?

According to article 2(2) (1) of the Clinical Trials Regulation, a clinical study is an 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; to ascertain the safety and/or efficacy of those medicinal products."

1.3. What is a 'low-intervention clinical trial'?

According to article 2 (2)(3) of the Clinical Trials Regulation, a low intervention clinical trial is defined as a clinical trial which fulfils all of the following conditions:

- "The investigational medicinal products, excluding placebos, are authorised.
- According to the protocol of the clinical trial, (i) the investigational medicinal products are used in accordance with the terms of the marketing authorisation; or (ii) the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned.
- The additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned.".

1.4. What can be considered as a 'non-interventional study'?

According to article 2(2)(4) of the Clinical Trials Regulation, a non-interventional study is defined as a "clinical study other than a clinical trial." Hence, a study is non-interventional as long as it does not fulfil any of the conditions defining a clinical trial.

1.5. How is a 'sponsor' defined?

Sponsors are defined in article 2(2)(14) of the Clinical Trials Regulation as "an individual, company, institution or organisation which takes responsibility for the initiation, management, and for setting up the financing of a clinical trial."

1.6. How is the 'start of a clinical trial' defined?

The Clinical Trials Regulation defines the start of a clinical trial in article 2(25) as to when "the first act of recruitment of a potential subject for a specific clinical trial" occurs. In this way, and unless differently defined in the protocol, the starting date of the clinical trial will be the date when recruitment for the clinical trial is opened in a Member State concerned.

1.7. What is considered to be an investigational medicinal product?

According to article 2(2)(5) of the Clinical Trials Regulation, an investigational medicinal product (IMP) is "a medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial."

2. Transitional period

2.1. Until when is the Clinical Trials Directive applicable?

According to article 96(1) of the Clinical Trials Regulation, the Clinical Trial Directive will be repealed on the day of entry into application of the Clinical Trials Regulation. After the application of the Clinical Trials Regulation, there will be however a transitional period that is defined in article 98 of the Clinical Trials Regulation. The transitional period foresees that the Clinical Trials Directive will still apply three years from the start date of application of the Clinical Trials Regulation to:

- Clinical trials applications submitted before the entry into application of the Clinical Trials Regulation.

- Clinical trials applications submitted within one year after the entry into application of the Clinical Trials Regulation, if the sponsor opts for the regime of the Clinical Trials Directive.

From the end of the third year since the entry into application of the Clinical Trials Regulation, only the Clinical Trials Regulation will apply, and all trials will have to switch to the Clinical Trials Regulation regime.

2.2. What will happen to those clinical trials that started before the date of entry into application of the Clinical Trials Directive and that have not been aligned with the requirements of the Clinical Trials Directive?

Such clinical trials do not benefit from the transitional provisions of the Clinical Trials Regulation. As a consequence, those trials cannot continue after the entry into application of the Clinical Trials Regulation. In case it is impossible to terminate a trial for reasons related to patient safety or scientific soundness, a sponsor should apply for a new authorisation for that trial under the Clinical Trials Regulation.[3]

2.3. At what point in time should the regulatory framework of a clinical trial switch from the Clinical Trials Directive to the Clinical Trials Regulation?

This possibility should be open from the day of the entry into application of the Clinical Trials Regulation until the end of the three-year transitional period, without the need to discontinue or put on hold a clinical trial. Sponsors should take into account the necessary time for the completion of the authorisation procedure under the Clinical Trials Regulation (at maximum 60 days).[4]

[3] Ibid, p. 99.

[4] Ibid.

2.4. What are the conditions for switching the regulatory framework of a trial from the Clinical Trials Directive to the Clinical Trials Regulation?

Only clinical trials that comply with the Clinical Trials Regulation as regards their substantial requirements can benefit from switching the regulatory framework of a trial from the clinical trials Directive to the Clinical Trials Regulation. In this sense, sponsors are responsible for assessing this compliance, and the Member States can take corrective measures, as foreseen in article 77 of the Clinical Trials Regulation if they identify that a trial, which has switched to the regulatory framework of the Clinical Trials Regulation, does not comply with the Clinical Trials Regulation.[5]

2.5. What are the consequences of switching the regulatory framework applicable to a clinical trial?

The Clinical Trials Regulation will govern the transitioned clinical trial from the moment of its (tacit) approval under the Clinical Trials Regulation. From this time point onwards, all requirements of the Clinical Trials Regulation will apply (e.g. obligations of notification, safety reporting rules, archiving requirements as well as the procedural rules of the Clinical Trials Regulation for requesting a substantial modification, the addition of a Member State)[6].

2.6. What if a clinical trial does not comply with the Clinical Trials Regulation?

If a trial does not comply with the Clinical Trials Regulation, a sponsor will need to request a substantial amendment under the Clinical Trials Directive before switching to the Clinical Trials Regulation regime, specifying its intention to align the trial with the Clinical Trials Regulation. Only after the substantial amendment has been accepted, the sponsor will be able to follow the procedures described below to switch the clinical trial to the Clinical Trials Regulation regime.[7]

2.7. How can a sponsor switch a clinical trial to the regulatory framework of the Clinical Trials Regulation?

According to article 5 of the Clinical Trials Regulation, the sponsor shall submit an initial application dossier through the Clinical Trials Information System (CTIS), but relying, in

[5] Ibid.

[6] Ibid, p. 103.

[7] Ibid, p. 100.

principle, on the existing dossier already assessed by the Member States. The process will require however a new cover letter and new application form (Part I and II) to be completed in CTIS and in case of multinational clinical trials, a harmonised or at least a consolidated protocol.[8]

3. Transparency

3.1. Will the assessment reports of clinical trial applications be made public at the time of decision?

According to article 81(4) of the Clinical Trials Regulation, the information in the EU database shall be made publicly available by default unless it is justified on specific confidentiality grounds (e.g. to protect personal data, commercially confidential information, or to protect confidential communication between Member States during the preparation of an assessment report). The assessment reports for Part I[9] and Part II[10] are in principle made public at the time of the decision. However, their publication can be deferred by the Responsible Member State (RMS) and Member State(s) concerned, respectively, in line with the deferral timelines defined by the sponsors at the time of submission of the initial application.[11]

3.2. When is the clinical trial data published and available to the general public?

The default option is always to make clinical trial data public at the earliest opportunity, in line with the Clinical Trials Regulation's aim to increase transparency of clinical trials and their results in the EU. However, unless there is an overriding public interest in disclosure, the data contained in an application dossier will not be publicly available until a decision on the clinical trial has been reached. As a general rule all data and documents in the system will be made public with few exceptions:

- Protection of personal data.
- Protection of commercially confidential information, in particular, taking into account the marketing authorisation status of the medicinal product, unless there is an overriding public interest in disclosure.

[8] Ibid.

[9] Article 6 of Regulation (EU) No 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use, *EU Official Journal* L158. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf

[10] Ibid, Art. 7

[11] European Commission, *Clinical Trials Regulation (EU) No 536/2014 Draft Questions & Answers*, version 4, July 2021, p. 30. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf

- Protecting confidential communication between Member States concerning the preparation of the assessment report.

- Ensuring effective supervision of the conduct of a clinical trial by Member States.

It should be noted that sponsors have the option to defer the timing of publication of specific data/documents (such as the protocol, the subject information sheet, the Investigational Medicinal Product Dossier (IMPD) or the Investigator's Brochure (IB)) up to 5 or 7 years post end of the trial. The summary of results of a clinical trial needs to be made public 12 months after the end of a trial, with a possibility of justified deferral in case of clinical trials on medicinal products (category I)[12] up to a maximum of 30 months post end of the trial (i.e. 18 months deferral).

[12] Kubiak C, de Andres-Trelles F, Kuchinke W, Huemer KH, Thirstrup S, Whitfield K, Libersa C, Barraud B, Grählert X, Dreier G, Grychtol R, Temesvari Z, Blasko G, Kardos G, O'Brien T, Cooney M, Gaynor S, Schieppati A, Sanz N, Hermandez R, Asker-Hagelberg C, Johansson H, Bourne S, Byrne J, Asghar A, Husson J-M, Gluud C, Demotes-Mainard J.Common definition for categories of clinical research for a survey on regulatory requirements by the European Clinical Research Infrastructures Network (ECRIN) Trials. 2009;10:95. doi: 10.1186/1745-6215-10-95.

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