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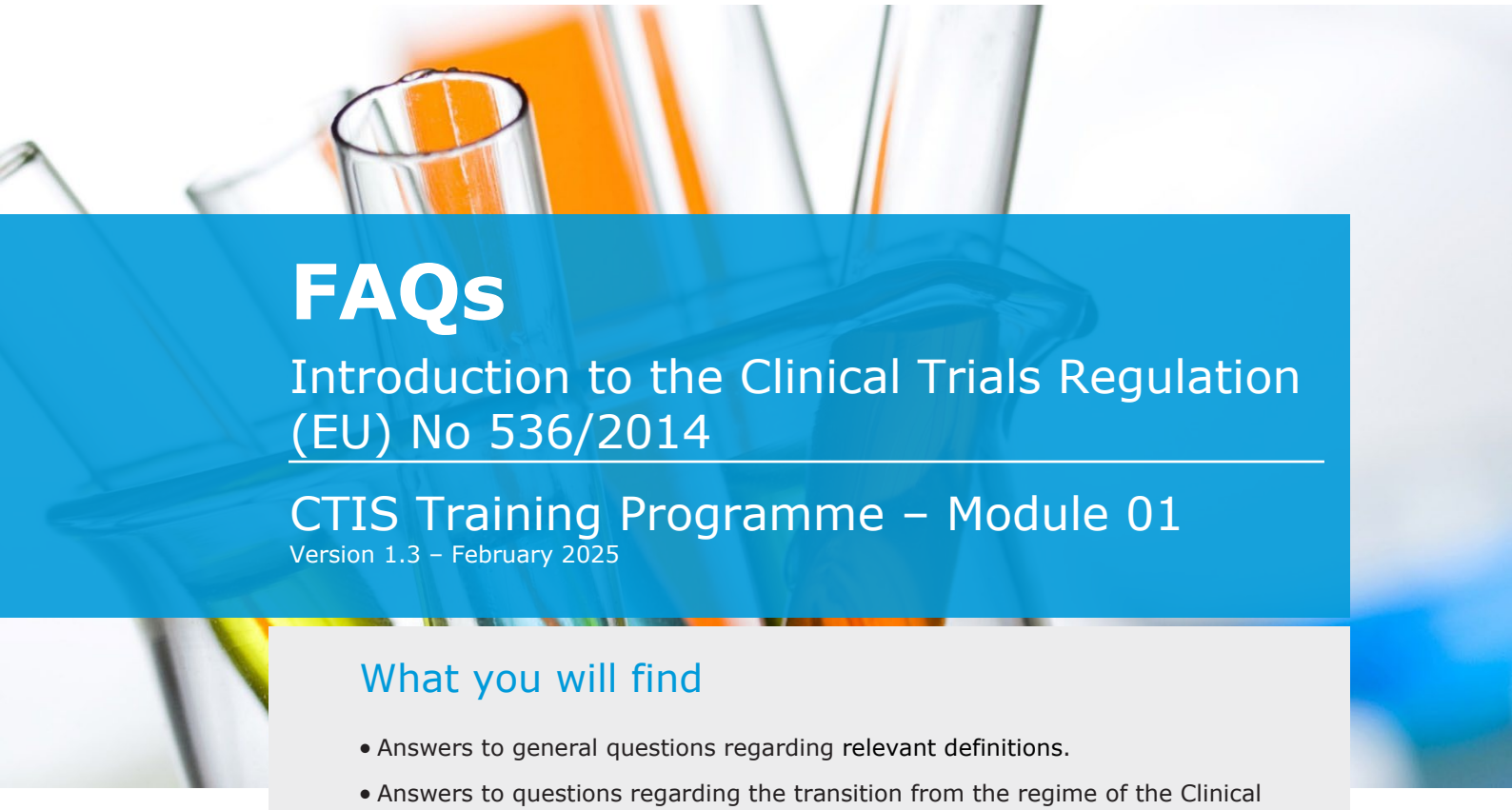

FAQs

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

CTIS Training Programme – Module 01

Version 1.3 – February 2025

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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Record of updated versions

The table below describes the updated versions after CTIS go-live (January 2022):

Version	Version description	Date
1.3	Removed questions: 2.3, 2.4, 2.6, 2.7, and 3.2 Updated questions: 2.1, 2.3, 3.1	February 2025
1.2	CTIS go-live version	October 2021

Contents

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."

Organisations that aim to create trials in CTIS need first to be registered in OMS. More details on requirements for sponsor organisations can be found in Module 03.

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 was the Clinical Trials Directive applicable?

According to article 96(1) of the Clinical Trials Regulation, the Clinical Trial Directive was repealed on the day of entry into application of the Clinical Trials Regulation. After the application of the Clinical Trials Regulation, there was a transitional period that was defined in article 98 of the Clinical Trials Regulation. The transitional period foresaw that the Clinical

Trials Directive still applied 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. What are the consequences of switching the regulatory framework applicable to a clinical trial?

The Clinical Trials Regulation governs 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 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)[4].

[3] Ibid, p. 99.

[4] Ibid, p. 103.

3. Transparency

3.1. Which data is made public under the Revised CTIS transparency rules and h Which are the publication rules for data and documents submitted to CTIS?

Data and documents submitted to CTIS are made available to the public as per the modality and timelines defined in the Annex 1[5] to the Guidance document on how to approach the protection of personal data and commercially confidential information while using the CTIS[6]. The detailed list of structured data that are or are not subject to publication is specified in the files CTIS application fields[7] and Notifications and Results[8]. A useful summary of the rules can be found in the quick user guide[9]. All the mentioned reference documents reflect the current publication rules for CTIS, defined in the Revised CTIS transparency rules[10], and provide guidance on the protection of personal data and commercially confidential information (CCI) submitted to the system, in accordance with the requirements of Article 81(4) of Regulation (EU) No 536/2014 (CTR). A Questions and Answers (Q&A) document on this topic is also available to users, see Q&A on the protection of Commercially Confidential Information and Personal Data while using CTIS[11].

[5] European Medicines Agency, *Annex I: Guidance document on how to approach the protection of personal data and commercially confidential information while using the Clinical Trials Information System (CTIS)*. Available at https://accelerating-clinical-trials.europa.eu/document/download/824905dd-3033-41e6-a871-67b20c4f4c94_en?filename=annex-i-guidance-document-how-approach-protection-personal-data-commercially-confidential_.pdf

[6] European Medicines Agency, *Guidance document on how to approach the protection of personal data and commercially confidential information while using the Clinical Trials Information System (CTIS) Version 2*. Available at https://accelerating-clinical-trials.europa.eu/document/download/6a0b836f-4779-4bb9-9584-1ce504a9ae38_en?filename=guidance-document-how-approach-protection-personal-data-commercially-confidential-information-while_.pdf

[7] European Medicines Agency, *CTIS application fields*. Available at: https://www.ema.europa.eu/en/documents/template-form/clinical-trial-information-system-ctis-structured-data-form-initial-application-additional-member-state-concerned-substantial-modification-non-substantial-modification_en.xlsx

[8] European Medicines Agency, *CTIS Structured data form - Notifications and Results*. Available at: https://www.ema.europa.eu/en/documents/template-form/clinical-trial-information-system-ctis-structured-data-form-notifications_en.xlsx

[9] European Medicines Agency, *Revised CTIS transparency rules and historical trials: quick guide for users*. Available at: https://accelerating-clinical-trials.europa.eu/document/download/a101771b-0be7-492f-b8bd-7f551ffbb7a7_en?filename=Revised%20CTIS%20transparency%20rules%2C%20Interim%20period%20%26%20Historical%20trials_quick%20guide%20for%20users_1.pdf

[10] European Medicines Agency, *Revised CTIS Transparency Rules*. Available at: https://www.ema.europa.eu/en/documents/other/revised-ctis-transparency-rules_en.pdf

[11] European Medicines Agency, *Q&A on the protection of Commercially Confidential Information and Personal Data while using CTIS* version 2.2. Available at: https://accelerating-clinical-trials.europa.eu/document/download/33702a5d-13be-4c4f-936d-3627dd73085b_en?filename=ACT%20EU_Q%26A%20on%20protection%20of%20Commercially%20Confidential%20Information%20and%20Personal%20Data%20while%20using%20CTIS_v1.3.pdf

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