



April 2018

The rules governing medicinal products in the European Union  
VOLUME 10 - Guidance documents applying to clinical trials

**CLINICAL TRIALS REGULATION (EU) NO 536/2014**

**DRAFT**

**QUESTIONS & ANSWERS**

**VERSION 1.0**

Submitted for discussion to the Expert Group on Clinical Trials.

*Note: Certain sections of this Q&A document are not yet complete. Updated versions of the Q&A will be published progressively.*

<b>Document history:</b>	
Date of discussion of draft by the expert group on Clinical Trials	Q&As were discussed progressively since December 2014. Final draft was finalised on 10 April 2018.
Date of publication:	20 April 2018
Date of entry into force:	On application of the Clinical Trials Regulation (EU) No 356/2014.
Supersedes:	N/A

**Keywords:** Clinical trials, Regulation (EU) No 536/2014, Questions and Answers

**Important notice:** The views expressed in this questions and answers document are not legally binding. Ultimately, only the European Court of Justice can give an authoritative interpretation of Community law.

All updates to this questions and answers document are presented and discussed within the “Expert group for clinical trials” and reflects the view of the group. This group is chaired by the Commission and is composed of representatives of all EU Member States and EEA contracting parties.



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## 1 THE SCOPE OF CLINICAL TRIALS REGULATION IN THE EU

### 1.1 **Question: What are the new characteristics of the Clinical Trials Regulation (EU) No 536/2014 as compared to the Clinical Trials Directive 2001/20/EC?**

1. **Answer:** The new Clinical Trials legislation has taken the legal form of a Regulation<sup>1</sup> and will replace national law. This will ensure that the rules for assessing clinical trial applications and for conducting clinical trials are identical throughout the EU. This is vital to ensure that Member States, in authorising and supervising the conduct of a clinical trial, base themselves on the same rules.
2. The Clinical Trials Regulation aims to create an environment that is favourable for conducting clinical trials, with the highest standards of patient safety, for all EU Member States. It will not only harmonize decisions, but also foster work sharing and collaboration between Member States
3. The main characteristics of the new Regulation are:
  - A streamlined application procedure via a single entry point - an EU portal and database, for all clinical trials conducted in EEA. Registration via the portal will be a prerequisite for the assessment of any application;
  - A single set of documents to be prepared and submitted for the application defined in Annex I of the Regulation;
  - A single authorisation procedure for all clinical trials, allowing a faster and thorough assessment of an application by all Member States concerned, and ensuring one single assessment outcome and authorisation per Member State;
  - A harmonised procedure for the assessment of applications for clinical trials, which is divided in two parts. Part I is jointly assessed by all Member States concerned. Part II is assessed by each Member State concerned separately;
  - Strictly defined deadlines for the assessment of clinical trial application;

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<sup>1</sup> OJ L 158, 27.05.2014 <https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:32014R0536>

- The involvement of the ethics committees in the assessment procedure in accordance with the national law of the Member state concerned but within the overall timelines defined by the Regulation;
- Simplified reporting procedures which will spare sponsors from submitting broadly identical information separately to various bodies and different Member States;
- Clinical trials conducted outside the EU, but referred to in a clinical trial application within the EU, will have to comply with regulatory requirements that are at least equivalent to those applicable in the EU;
- Strengthened transparency for clinical trials data;
- A coordination and advisory committee that will serve as a forum for exchanging best practices between Member States;
- Union controls in Member states and third countries to ensure that clinical trials rules are being properly supervised and enforced.

## **1.2 Question: Till when is the Clinical Trial Directive 2001/20/EC applicable?**

4. **Answer:** Directive 2001/20/EC will be repealed on the day of entry into application of the Clinical Trials Regulation (EU) No 536/2014. It will however still apply three years from that day to:
- Clinical trials applications submitted before the entry into application of Regulation (EU) No 536/2014 and
  - Clinical trials applications submitted within one year after the entry into application of Regulation (EU) No 536/2014, if the sponsor opts for the old system.

## **1.3 Question: What is a “clinical trial”?**

5. **Answer:** Article 2(2) (1 and 2) of the Clinical Trials Regulation provides a definition of a "clinical study" as well as a “clinical trial”:
- A ‘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.
- The decision tree in Annex II can be used to identify whether a trial is a clinical trial in the sense of Regulation (EU) No 536/2014.

#### **1.4 Question: What is a "low-intervention clinical trial"?**

6. **Answer:** A "low intervention clinical trial" is defined in Article 2 (2)(3) of the Clinical Trials Regulation as a clinical trial which fulfils all of the following conditions:
  - (a) the investigational medicinal products, excluding placebos, are authorised;
  - (b) 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; and
  - (c) 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;
7. The decision tree in Annex II can be used to identify whether a trial is a low-intervention clinical trial in the sense of the Clinical Trials Regulation.

#### **1.5 Question: What can be considered as a "non-interventional study"?**

8. **Answer:** According to Article 1 of the Clinical Trials Regulation, non-interventional studies are excluded from the scope of this Regulation.
9. A "non-interventional study" is defined in Article 2(2)(4) of the Clinical Trials Regulation as "a clinical study other than a clinical trial".
10. Thus, a study is non-interventional if it does not fulfil any of the following conditions which define a Clinical Trial (according to Article 2 (2)(2) of the Clinical Trials Regulation:

- 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.
11. The decision tree in Annex II can be used to identify whether a trial is a non-intervention clinical trial in the sense of Regulation (EU) No 536/2014.
12. The purpose for excluding these trials from the scope of the Regulation (EU) No 536/2014 is that these trials are typically considered to have the lowest risk. Moreover, this restriction shall ensure that medical activities which are normal clinical practice and as such, part of the general medical surveillance of a patient, are excluded from the scope of the Regulation (EU) No 536/2014.

**1.6 Question: Is the definition of 'medicinal product' relevant for the scope of the Clinical Trials Regulation?**

13. **Answer:** Yes.
14. When assessing whether a study is a clinical trial as defined in Regulation (EU) No 536/2014, the first question is always whether the object of the study is a medicinal product (see also the algorithm in Annex II).
15. 'Medicinal product' is defined in Article 1(2) of Directive 2001/83/EC. Article 1(2) of the Medicinal Products Directive defines "medicinal product" as follows: "(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or (b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis."
16. A substance is thus a medicinal product either by virtue of its "presentation" or its "function". A substance constitutes a medicinal product if it falls within either of these two categories.
17. To establish the 'borderline' between a medicinal product and other products, the established criteria, as further explained in detailed Commission guidance apply. Such Commission guidance exists in particular for the borderline

- Medicinal product – cosmetic product;<sup>2</sup> and
  - Medicinal product – medical device<sup>3</sup>
  - Medicinal product - food supplements<sup>4</sup>
18. With regard to a medicinal product by "virtue of function", in some cases it may not be 100% certain whether the product which is object of the study exerts a pharmacological, immunological or metabolic action. The term "medicinal product", as read in the context of the Clinical Trials Regulation should also encompass the products where the pharmacological, immunological, or metabolic action is still uncertain and being explored.
19. This includes also medicinal products which are specifically addressed in the EU law on pharmaceuticals, such as advanced therapy medicinal products<sup>5</sup> or medicinal products derived from human blood or human plasma as defined in Article 1(10) of Directive 2001/83/EC.
20. The Regulation also applies to interventional clinical trials with medicinal products for the paediatric population and interventional clinical trials with medicinal products manufactured or reconstituted in a (hospital) pharmacy and intended to be supplied directly to the clinical trials participants.
21. To draw the 'borderline' between these sectoral legislations (e.g. medicinal products/food, medicinal products/cosmetic products, medicinal products/medical devices), the established criteria as set out in the case law of the European Court of Justice apply and reference is made to the relevant guidelines<sup>6</sup>.

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<sup>2</sup> [available](https://ec.europa.eu/growth/sectors/cosmetics/products/borderline-products_en) here [https://ec.europa.eu/growth/sectors/cosmetics/products/borderline-products\\_en](https://ec.europa.eu/growth/sectors/cosmetics/products/borderline-products_en)

<sup>3</sup> [https://ec.europa.eu/growth/sectors/medical-devices/guidance\\_en](https://ec.europa.eu/growth/sectors/medical-devices/guidance_en)

<sup>4</sup> DIRECTIVE 2002/46/EC published on 10 June 2002 at <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32002L0046&from=EN>

<sup>5</sup> As defined in Article 2(1)(a) of Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L 324, 10.12.2007, p. 121) (hereinafter Regulation (EC) No 1394/2007).

<sup>6</sup> cf., for example, [http://ec.europa.eu/growth/sectors/cosmetics/products/borderline-products/index\\_en.htm](http://ec.europa.eu/growth/sectors/cosmetics/products/borderline-products/index_en.htm)

**1.7 Question: A study might involve the administration of a medicinal product, while the object of the investigation is not the administered medicinal product, but exclusively the physiology of the body. Are these studies 'clinical trials' as defined in Regulation (EU) No 536/2014?**

22. **Answer:** No.
23. There may be studies which have as the only object to investigate the physiology of the body. In these studies, a medicinal product is administered only in order to obtain a physiological response in order to study the physiology of the body, i.e. without the medicinal product itself being the object of the investigation. Rather, the medicinal product is administered to provoke a pharmacological response which is needed to study the physiology of the body.
24. Examples are a study of the physiology of the retina where a pupil dilator may be used in order to enable the study of the physiology of the retina. Another example is the use of a vasodilator to study how the endothelial function is affected by disease (or other factors not including medicinal products), the use of diagnostic agents to study the effect of disease (or other factors not including medicinal products) or the use of a challenge agent to study the effect of disease (or other factors not including medicinal products). This issue is also relevant for radiopharmaceuticals used as diagnostic agents (see Q1.8).
25. These studies are not 'clinical trials' as defined in article 2(2)(2) of Regulation (EU) No 536/2014. Consequently, the medicinal product administered is not an investigational medicinal product as defined in article 2 (2)(5) of Regulation (EU) No 536/2014.
26. These studies are not regulated at EU-level. It is up to Member States to decide whether and how they to regulate these studies. For medicinal products that do not have a marketing authorisation, the desired pharmacological response should be corroborated by published scientific evidence on safety and efficacy in humans, supporting the chosen dose level and route of administration.
27. However, care has to be taken as to whether the object of an investigation is being 'switched', in the course of a study, from the physiology of the body to the pharmacological effect triggered by the medicinal product. In this case, a study may 'turn into' a clinical trial which falls within the scope of Regulation (EU) No 536/2014, provided it is not non-interventional (defined in article 2 (2)(4) of Regulation (EU) No 536/2014).

**1.8 Question: How does the issue set out in Question 1.6 apply to PET studies?**

28. **Answer:** A radiopharmaceutical used as diagnostic agent in a positron emission tomography (PET) study is a medicinal product.
29. If the object of the study is the diagnostic potential of the diagnostic agent, the study is a clinical trial and the diagnostic agent is the investigational medicinal product (IMP).
30. Studies may have as object a medicinal product 'A' (radiopharmaceutical or other) while, in addition, a diagnostic agent 'B' is used to study the effect of the medicinal product 'A'. In this case, the study is a clinical trial. In this study, the medicinal product 'A' is an investigational medicinal product as defined in article 2 (2)(5) of Regulation (EU) No 536/2014. However, the medicinal product 'B' is not an investigational medicinal product as defined in article 2 (2)(5) of the Clinical Trials Regulation.
31. If the object of the study is only a physiological characteristic where the PET is merely used to study that characteristic, i.e. there is no medicinal product being the object of the study, the study is not a clinical trial. These studies are not regulated at EU-level. It is up to Member States to decide whether and how they to regulate these studies.

**1.10 Question: Is a study addressing the time of surgery a clinical trial, if patients receive otherwise standard treatment with medicines?**

36. **Answer:** This is a case by case decision and it depends on whether the object of the study is one of those listed in article 2 (2)(1) of the Clinical Trials Regulation and whether it fulfils the conditions in article 2 (2)(2) of the Regulation. If this is not the case, the study is not a clinical trial. The sponsor has the responsibility to provide clear information on the object of the study.

**1.11 Question: Does the Clinical Trials Regulation apply to clinical trials with IMPs which fall under the 'hospital exemption' for advanced therapy medicinal products?**

37. **Answer:** Yes. The 'hospital exemption' for advanced therapy medicinal products, which is contained in article 3(7) of the Directive 2001/83/EC<sup>11</sup> is irrelevant for the scope of the Clinical Trials Regulation. Regulation (EU) No 536/2014 applies to any clinical trial with advanced therapy investigational medicinal products (see definition in article 2(2)(7) of the Regulation).

**1.12 Question: Is an authorised medicinal product used as comparator in a clinical trial considered to be an investigational medicinal product?**

38. **Answer:** Yes. 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*".
39. Comparators are medicinal products used as a reference in a clinical trial vis-à-vis the substance being tested.
40. The purpose for the inclusion of comparators into the definition of IMP is that they play a fully equivalent, symmetric role as counterparts to the

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<sup>11</sup> As amended by Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004.

“tested products”, and this from the inception of the protocol to the interpretation of the study results. The comparator is an IMP and the conditions (circuit, storage, traceability, return, destruction and accountability methods) under which the comparator is used are to be strictly the same as those of the “tested product”, taking into account whether the IMP is an authorised IMP and whether the clinical trial is a low-intervention trial.

### **1.13 Question: What are the regulatory requirements for IMPs?**

41. **Answer:** Regarding IMPs there are a number of regulatory requirements. Note, however, that the regulatory framework is adapted to situations where the IMP is used in the authorised form and for the authorised indication. This holds in particular for:
- the information requirements for request for authorisation to be submitted to the national competent authority of the Member State concerned; and
  - the requirements for the labelling of IMP a set out in articles 66-69 of Regulation (EU) No 536/2014. (See also question 2.6).

### **1.14 Question: What is considered to be an auxiliary product?**

42. **Answer:** Investigational medicinal products shall be distinguished from auxiliary medicinal products. Auxiliary medicinal products are used in the context of a clinical trial as described in the protocol<sup>12</sup> for background treatments, as challenging agents, rescue medication or to assess the end-points. (See also section 8 of this Q&A on "*Authorisation of manufacturing and importation of IMPs*" and the recommendations of the expert group on clinical trials on "*Auxiliary medicinal products in clinical trials*", rev. 2, June 2017<sup>13</sup>).
43. The documentation requirements set out in sections F and G of Annex I of the Clinical Trials Regulation also apply to auxiliary medicinal products. However, where the auxiliary medicinal product is authorised in the Member State concerned, no additional information apart from a valid SmPC is required.

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<sup>12</sup> Article 2(2)(8) of Regulation (EU) No 536/2014

<sup>13</sup>[https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017\\_06\\_28\\_recommendation\\_on\\_axmps.pdf](https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017_06_28_recommendation_on_axmps.pdf)

44. In principle, only authorised medicinal products should be used as auxiliary medicinal products in clinical trials (article 59 of the Clinical Trials Regulation). However, in certain circumstances unauthorised auxiliary medicines may be used. This has to be justified in the protocol. The acceptable reasons for admitting non-authorised auxiliary medicinal products would be related to the availability of authorised auxiliary medicinal products (e.g. no authorised medicinal products exist in the EU, or the amounts available are not sufficient to satisfy the need of the clinical trial). The lower price of non-authorised auxiliary medicinal product shall not be considered as a legitimate justification.<sup>14</sup>).

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<sup>14</sup> Recital 53 of Regulation (EU) No 536/2014

### **1.16 Which principles of Good Laboratory Practice (GLP) need to be taken into account in clinical trials?**

50. **Answer:** In accordance with article 25 (3) of the Clinical Trials Regulation, non-clinical information submitted in an application dossier shall be based on data derived from studies complying with Union law on the principles of good laboratory practice (GLP) as laid out in Directive 2004/10/EC, as applicable at the time of performance of those studies.
51. Therefore these studies must be conducted in a test facility that is part of the national GLP monitoring programme of an European Union (EU) Member State, Organisation for Economic Co-operation and Development (OECD) Member Country or fully adherent to the Mutual Acceptance of Data (MAD), and found in compliance with the principles of GLP.
52. Studies conducted at a facility located in a non-MAD adherent country may be accepted if the facility has been subject to a full monitoring inspection conducted by a monitoring authority from an EU member state country, OECD Member Country or full adherent to the MAD agreement and found to be compliant at the time the data was generated. However if the study is considered to be pivotal to the application, there is a possibility that a study audit will be required by some regulatory receiving authorities at the time an investigational medicinal product dossier (IMPD) is received or at the time the Marketing Authorisation Application (MAA) is reviewed.
53. Sponsors should include a statement confirming the GLP status of the studies or equivalent standards (i.e. principles of GLP recognised by other countries) within the IMPD (Annex I point 44), unless properly justified.
54. A summary table should be provided, listing the non-clinical studies and indicating the following for each study:
  - (1) study title,
  - (2) study code (Unique identifier assigned to the study),
  - (3) date of completion of the Final Report,
  - (4) test facility and test sites in which the study was conducted,
  - (5) complete address of the test facility (and test sites where applicable),
  - (6) period in which the test facility(ies) and/or test site(s) was (were) used
55. Sponsors should also indicate if in that period the facility was part of an European Union (EU) or an Organisation for Economic Co-operation and Development (OECD) Mutual Acceptance of Data (MAD) - accepted GLP monitoring programme.

### **1.17 Which principles of Good Laboratory Practice (GLP) need to be taken into account in relation to Advanced Therapy Medicinal Products (ATMPs)?**

56. **Answer:** It is generally expected that non-clinical safety studies are carried out in conformity with the principles of good laboratory practice (GLP). However, it is recognised that, due to the specific characteristics of ATMPs, it would not always be possible to conduct these studies in conformity with GLP. Exploratory pre-clinical studies, where safety information is obtained alongside with other information (e.g. in dose finding studies), are also not expected to be conducted under GLP.
57. If a pivotal non-clinical safety study<sup>15</sup> has not been conducted in conformity with the GLP principles, a proper justification should be submitted. This justification should also address the potential impact of the non-compliance on the reliability of the safety data.
58. When pivotal non-clinical safety studies are not conducted in compliance with GLP, detailed documentation of study conduct and archiving of data should be ensured. Additionally, the conduct of the study should be in accordance with a prospectively designed study protocol. A summary of deviations from the protocol and their potential impact on the outcome of the study should be included in the relevant study report. The sponsor of the non-clinical study should consider appointing a person responsible for the oversight of the conduct of the study and the study reports.
59. Applicants who submit pivotal safety studies that are non-GLP compliant in the context of an application for a clinical trial or a marketing authorisation may be asked to submit additional data to justify the reliability of the studies or to permit a site visit to verify the conditions under which the study has been conducted.

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<sup>15</sup> The term “pivotal non-clinical safety studies” refers to toxicity studies which support the non-clinical safety conclusions. Among others, the following are *not* considered non-clinical *safety* studies: basic research (primary and secondary pharmacology), proof of concept studies, dose response studies, analytical quality control testing for clinical and commercial studies, stability testing on commercial products and feasibility studies.

**2 APPLICATIONS LIMITED TO PART I (ARTICLE 11 OF REGULATION (EU) NO 536/2014), ADDITIONAL MEMBER STATE (ARTICLE 14 OF REGULATION (EU) NO 536/2014) AND OTHER MEASURES RELATED TO THE APPLICATION PROCEDURE**

**2.1 Question: Is it possible for a sponsor to submit a whole application (Part I and II) to some Member States concerned (on the basis of article 5) at the same time as an application limited to Part I only (on the basis of article 11) to other Member States concerned?**

60. **Answer:** Yes. Such a mixed application is permitted.
61. It implies that the Member States in which the sponsor submitted the whole application (Part I and Part II) would assess the whole dossier on the basis of articles 5, 6 and 7 of the Regulation (aspects covered by Part I and II), and after the positive decisions by these Member States concerned (MSC) are issued a clinical trial can start in those MSC.
62. The other MSC covered by an application limited to Part I only assess the aspects covered by Part I on the basis of article 5 and 6, together with the MSC who received the full application.
63. The conclusion on Part I with regard to the latter Member States is valid for 2 years and the sponsor can during this period submit the additional part II to the respective MSC (refer to Q2.2 for further details). Only when MSC have issued the positive decision on the full application (Part I and Part II) the sponsor can start the trials in these MSC. If within 2 years the sponsor does not submit Part II in these Member States, the aspects covered by Part I of the clinical trial application shall be deemed to have lapsed with respect to these Member States.

**2.2 In cases of applications limited to Part I (article 11) how should a sponsor proceed to submit an application for Part II?**

64. **Answer:** Following the notification of the conclusion on Part I, but only during the subsequent 2 years, a sponsor may submit an application for aspects covered by Part II of the assessment report, declaring that he is not aware of any new substantial scientific information that would change the validation of any item submitted in the application on aspects covered by Part I which were already assessed by the Member States concerned (MSC). The list of the documentation and information required is set out in Annex I and shall be limited to sections K to R of this Annex.
65. However, if at this stage the sponsor becomes aware of the need for a substantial modification of Part I, two scenarios are possible, depending on whether a trial has already been authorized in at least one MSC or not.

- In case a clinical trial has been authorized in at least one MSC, the sponsor has to first submit an application for a substantial modification to all MSC (i.e. those MSC covered by the full application as well as those MSC limited only to Part I). Once the decision on the substantial modification is issued by at least 1 MSC covered by a full application, the sponsor can then submit Part II to those MSC with an application limited to only Part I (see also Q3.4).
- However in case an application was submitted on a basis of article 11 with regards to all MSC and no Part II has been submitted for assessment to any MSC, the sponsor should withdraw the application from all MSC and resubmit it, indicating the substantial modifications in the cover letter.

### **2.3 When is it possible for a sponsor to submit an application for the subsequent addition of a Member State (article 14 of the Clinical Trials Regulation)?**

66. **Answer:** An application for the extension of a clinical trial to another Member State can only be submitted after the clinical trial has been authorized, after the date on which the sponsor has been notified of the initial authorization decision. This means that the request can be submitted after at least 1 Member State has issued a positive decision (in accordance with article 8).
67. This implies that in cases when a sponsor has submitted an application for a clinical trial limited to Part I only (on the basis of article 11), an application for an additional Member State cannot be submitted. This can only happen after Part II has been submitted and the clinical trial approved, in at least 1 Member State.
68. If the assessment of an application for an additional Member State is ongoing, an application for a substantial modification of the clinical trial cannot be submitted (see Section 3).

### **2.4 Question: After the receipt of the decision on the clinical trial, does the sponsor have the option to appeal against the decision?**

69. **Answer:** The Clinical Trials Regulation states that Member States shall provide an appeal procedure in respect of a refusal related to articles 8, 14, 20 and 23. The respective national laws apply.

### **2.5 Question: Where an application for a clinical trial is submitted in more than one Member State, does a sponsor have to await positive decisions from all Member States concerned, before commencing the trial in any of the Member States concerned?**

70. **Answer:** No.

71. The sponsor/investigator can commence a clinical trial in the Member State concerned if a positive decision on both Part I and II of the assessment report has been issued by the Member State concerned.

**2.6 Question: Chapter X and Annex VI of the Clinical Trials Regulation refer to the content of the labelling of the investigational medicinal product (IMP). Does this mean a mock-up needs to be submitted?**

72. **Answer:** No.
73. Only the text that is labelled on the IMP, as per Chapter X and Annex VI of the Clinical Trials Regulation, should be included in the application dossier.

### 3 SUBSTANTIAL MODIFICATIONS

#### 3.1 Question: How is a "substantial modification" defined?

74. **Answer:** Article 2(2)(13) of The Clinical Trials Regulation defines a substantial modification as " any change to any aspect of the clinical trial which is made AFTER notification of a decision referred to in articles 8, 14, 19, 20 or 23 and which is likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial". This implies that a substantial modification (SM) can be submitted and assessed only after a decision is issued on a previously submitted application: initial application (article 8), additional member state (article 14), another SM on Part I only or Part II only or both Part I and II (articles 19, 20 and 23) (see also Q2.2).
75. Since no applications for a SM of the dossier can be submitted while another assessment is ongoing (be it assessment of an initial application, a request for another SM or to add an additional Member State), only an application for a SM of Part II can be submitted in parallel to that submitted in a different Member State concerned (MSC) (i.e. an application for a SM of Part II in a MSC can be submitted while the assessment of another SM for Part II is ongoing in another MSC).
76. Information on any changes to a clinical trial which are not SMs but are relevant for the supervision of the clinical trials by the Member States concerned shall be permanently updated in the EU database by the sponsor, in line with article 81(9) of Regulation (EC) No 536/2014.
77. For a non-exhaustive list of examples of substantial and non-substantial modifications, please see Annex I.

#### 3.2 Question: What is understood by the notion of ‘substantial’?

78. **Answer:** Modifications to a trial are regarded as ‘substantial’ when they are likely to have a significant impact on:
- the safety or rights of the subjects and/or
  - the reliability and robustness of the data generated in the clinical trial.
79. In all cases, a modification is regarded as ‘substantial’ when one or both of the above criteria are met. It is, in principle, the responsibility of the sponsor to assess whether a modification is to be regarded as ‘substantial’. This assessment is to be made on a case-by-case basis in view of the above criteria. For a non-exhaustive list of examples of substantial and non-substantial modifications please see Annex I.

80. The sponsor should assess also whether a substantial modification (or the combination of a number of substantial modifications) leads to changes in the clinical trial to an extent that it has to be considered as a completely new clinical trial, which would require an application for a new trial authorisation. For example, a change of the investigational medicinal product (IMP), certain significant modifications, such as a change to the main objective or primary end point of the clinical trial in all phases, as well as the unplanned and unjustified addition of a trial arm or placebo group (except in the exceptional case of a clinical trial with a novel design, where this was already described in the protocol of the initial application) are considered as resulting in a new clinical trial and not as substantial modifications and would therefore require a new trial authorization.
81. Based on the criteria mentioned in point 78, it can be acknowledged that not every change to the clinical trial application is by default to be considered as a '*substantial*' modification. The sponsor should however notify to Member States concerned any changes to a clinical trial which are not substantial modifications but are relevant for the supervision of the clinical trials by updating the information in the EU database (see point 76).

### **3.3 Question: When can a sponsor submit a substantial modification concerning Part I and II?**

82. **Answer:** The definition of a substantial modification (SM) in the Clinical Trials Regulation (article 2(2)13) implies that a SM request can be considered only after the decision on the clinical trial is taken in at least one Member State (see Q3.1) This implies that no SM request can be assessed while any assessment is on-going (be it an assessment of an initial application, a request to add a Member State concerned (MSC) or a request for another SM). Therefore, the SM can be assessed only after the decision on the previously submitted application is issued.

### **3.4 Question: Is a sponsor allowed to submit a substantial modification concerning Part I in those Member States where an application was originally submitted for only Part I (limited application on the basis of article 11)?**

83. **Answer:** In case of mixed applications (i.e. applications submitted in some of the Member States Concerned (MSC) on the basis of article 11 (Part I only) while in other MSC on the basis of article 5 (full dossier, Part I and II)), the assessment of a substantial modification (SM) of Part I has to take place in all MSC (on the basis of article 5 as well as on article 11), on the condition that:

- At least one MSC with a full application (article 5) has communicated already its decision to authorise the initial application.
  - No other assessment is ongoing, which means that the sponsor did not submit in the meantime an application for the assessment of Part II in any of the Member States covered by the limited application or an application for an additional MS.
84. The submission and assessment of a SM concerning Part I should take place in all Member States that have issued positive conclusions on Part I.
85. Any on-going assessment of Part II in any of the Member States covered by the limited application, would make the assessment of a SM of Part I impossible with regards to all MSC.

**3.5 Question: How should a sponsor proceed in case a substantial modification is required while the assessment of another application for the same clinical trial is ongoing (under evaluation)?**

86. **Answer:** In case the sponsor realises that a substantial modification (SM) may be needed while any assessment is still on-going he can, depending on the urgency of that need:
- wait for the on-going assessment to end before submitting the SM;
  - withdraw the on-going application and introduce the SM (see also Q3.1 and Q4.3).
87. If urgent safety measures are required while any assessment is still ongoing, the sponsor should take the appropriate measure and notify the MSC. A SM can then be submitted once the ongoing SM is finalised.

**3.6 Question: How should a sponsor proceed when a substantial modification is related to a document common to various clinical trials of the same sponsor and same IMP?**

88. **Answer:** In cases of substantial modifications (SM) related to the investigational medicinal product dossier (IMPD) (Quality, safety or efficacy), to the investigator's brochure (IB), reference safety information or any other common document used in multiple clinical trials it is recommended to submit these modifications for authorization as a single request for all clinical trials of the same sponsor and IMP for efficiency and consistency purposes (see Annex II of the Clinical Trials Regulation). To ensure harmonization of documents common to various Clinical Trials the

cover letter shall list all the clinical trials to which the application for the SM applies together with the EU trial numbers (see additional requirements in Annex II of the Clinical Trials Regulation) and their responsible RMS.

89. Additionally the sponsor may submit in an initial application the same IMPD and IB (or other relevant documents) that was previously submitted in an application for an on-going trial or for an application that is being/has been evaluated (e.g an on-going/completed assessment of an initial application, a SM or an additional member state application). In such an event, it is recommended that reference to these applications is made in the cover letter and the EU trial number of reference should be recorded as structured data in the initial application.

**3.7 Question: Is the addition of an additional Member State considered to be a substantial modification?**

90. **Answer:** No. The subsequent addition of another Member State concerned to extend an authorised clinical trial requires the submission of an application dossier in accordance with article 14 of Regulation (EU) No 536/2014. An application dossier in this regard may be submitted only after the notification date of the initial authorisation decision (see also Q2.3).

**3.8 Question: Is the deletion of a Member State considered to be a substantial modification?**

91. **Answer:** The deletion of a Member State concerned is not recognized by the Clinical Trials Regulation and is not considered to be a substantial modification.
92. Various scenarios are possible to deal with such cases:
- Scenario 1: *The sponsor decides to withdraw an application for a clinical trial in a MSC.* This may happen at any time until the decision is made, providing reasons. However in cases of withdrawal of an application before the reporting date, the withdrawal will apply to the entire application in all Member States concerned (MSC). After the reporting date, but before the decision is taken by a particular MSC, the sponsor has the option to withdraw the application in one, two or all MSC.
  - Scenario 2: *The sponsor decides to withdraw an application in case of mixed applications* (see Q2.1). Scenario 1 above applies also in this case. However additionally, in the case of MSC that received only an application limited to Part I, an application could be withdrawn at any point after the reporting date (article 6(6) of the Clinical Trials Regulation)

even if the clinical trial is already authorised in one or more of the other MSC that received a full application.

- Scenario 3: *The sponsor decides to terminate early an ongoing clinical trial in one of the Member States concerned* (i.e. after the decision is issued in that MSC). The sponsor should notify the MSC of the early termination (see Section 10). In case of early termination due to reasons of the subjects' safety (article 38(1) of Regulation (EU) No 536/2014), the notification shall be made without undue delay but not later than 15 days from the date of the early termination. Early termination in such cases in principle would apply to all MSC. In case of early termination for reasons not affecting the benefit-risk balance, the Regulation does not set up a timeline for such notification but requires that the sponsor informs each Member State concerned of the reasons for such action and, where appropriate, on the follow up measures for the subjects (article 37(7)).

93. In all cases described above, that is, i) when a clinical trial application is withdrawn from a Member State concerned (scenarios 1 and 2) or ii) if the clinical trial in a MS is terminated early (scenario 3), while the clinical trial is ongoing in other MSC, scientifically, the sponsor should assess the potential impact on the overall recruitment/sample size of the clinical trial and submit a substantial modification to the other MSC if necessary (e.g. to add more sites in MSC).

### **3.9 Question: Is the annual safety report considered to be a substantial modification?**

94. **Answer:** No. The annual safety report (ASR) submitted in the Eudragilance database in accordance with article 43 of The Clinical Trials Regulation is not *per se* an amendment and thus does not have to be notified as a substantial modification to the Member State concerned. However, the sponsor has to verify whether the data presented in the ASR requires a change to the documentation submitted with the request for authorisation of a clinical trial. If this modification is substantial, the rules for notification of substantial modifications apply to these changes.

### **3.10 Question: Is a change of the Principal Investigator considered to be a substantial modification?**

95. **Answer:** Yes
96. Article 15 of The Clinical Trials Regulation specifies that the change of a principal investigator may only be implemented in accordance with the procedure for a substantial modification of a clinical trial.

## 4 WITHDRAWALS

### 4.1 **Question: In which circumstances can a sponsor withdraw an application for a clinical trial?**

97. **Answer:** The sponsor has the option to withdraw an application for a clinical trial at any time until the decision is made.
98. However in cases of withdrawal of an application before the reporting date (article 6(6) of the Clinical Trials Regulation), the withdrawal will apply to the entire application in all Member States concerned.
99. After the reporting date, but before the decision is taken by a particular Member State concerned, the sponsor has the option to withdraw the application in one, two or all Member States concerned
100. In cases when the procedure of article 11 is applied and Part II is submitted later to one or more Member States concerned (within the 2 year period), the application for Part II can be withdrawn from one or more Member States concerned. The sponsor can also withdraw the entire application (also the previously submitted Part I) if he so chooses, until the decision is made.
101. Once the decision regarding an application is taken a sponsor no longer has the possibility to withdraw this application. If a CT does not start and the sponsor decides not to carry out the clinical trial in a Member State concerned, the application will expire after 2 years from the notification date of the authorisation. Otherwise once the CT starts, it may be a case of early termination if it does not proceed. (Please refer to section 10 for more information).

### 4.2 **Question: Can an application be re-submitted?**

102. **Answer:** After a withdrawal has taken place, re-submission is possible.

### 4.3 **Question: In which circumstances can a sponsor withdraw an application for a substantial modification of a clinical trial?**

103. **Answer:** Withdrawal of an application for a substantial modification of the clinical trial is possible:
- In the case of a substantial modification of Part 1 or Part I and Part II, the withdrawal applies to all Member States concerned and can take place at any point during the assessment until the decision is issued;

- In the case of a substantial modification of Part II only, an application can be withdrawn from one or more Member States concerned, at any point during the assessment until the decision is issued.
104. These possibilities for withdrawal allow the sponsor to withdraw an application in cases such as an urgent safety measure or if other substantial modifications are required. Therefore a sponsor may choose not to wait for the end of the assessment of an ongoing application for a substantial modification and withdraw the application to submit a new one, with the updated substantial modification (see Q3.5).

## 5 SPONSOR/LEGAL REPRESENTATIVE; INVESTIGATOR

### 5.1 Question: How is “sponsor” defined?

105. **Answer:** “Sponsor” is defined in article 2(2)(14) of The Clinical Trials Regulation as “an individual, company, institution or organization which takes responsibility for the initiation, management and for setting up the financing of a clinical trial.”
106. Thus, the sponsor can be an individual, a company, an institution or an organisation. Article 71 states that a trial may have one or more sponsors. A loose, informal networks of researchers and research institutions may jointly conduct a clinical trial as co-sponsors.
107. Article 71 also clarifies that sponsor and investigator may be the same person. The sponsor does not need to be located in an EU Member State. (See also Q5.6)

### 5.2 Question: How are responsibilities shared in case of co-sponsorship?

108. **Answer:** In case a clinical trial has more than one sponsor, all co-sponsors shall in principle have the responsibilities of the sponsor (article 72 of Regulation (EU) No 536/2014). This implies that all of them are jointly responsible (e.g. also for the safety issues) and a Member State concerned may expect the execution of a sponsor's obligations from any of the co-sponsors.
109. However, the co-sponsors shall jointly determine, in a written contract which sponsor will be responsible for the following tasks:
- compliance with a sponsor's obligations in the authorisation procedure (including any substantial modification and the procedure for the addition of a Member State concerned);
  - a contact point for receiving questions from subjects, investigators or any Member State concerned regarding the clinical trial and for replying to them;
  - implementing corrective measures imposed by any of the Member states concerned.
110. Each task mentioned above can be attributed to only one sponsor. Co-sponsors cannot have a joint responsibility for the same task mentioned above. This means that the responsibility for compliance with each of the above tasks will lie with only one sponsor and cannot be shared between the different sponsors.

111. The co-sponsors may split up all remaining responsibilities by contractual agreement. If they do not do this, the principle of joint responsibility applies.

**5.3 Question: Is the person financing a clinical trial always considered as “sponsor” in the sense of article 2(2)(14) of Regulation (EU) No 536/2014?**

112. **Answer:** A sponsor is defined in article 2(2)(14) of the Clinical Trials Regulation as “an individual, company, institution or organisation which takes responsibility of the initiation, for the management and for setting up the financing of a clinical trial”.
113. Every clinical trial has to have a sponsor.
114. In light of the definition, the sponsor is the person who presents himself as the person taking the responsibility for the clinical trial. The sponsor would as well be responsible for setting up financial arrangements allowing the conduct of clinical trial (this does not however mean necessarily by funding it him/herself). The person funding a clinical trial *may* however be the sponsor.

**5.4 Question: Can the sponsor delegate tasks/functions?**

115. **Answer:** The sponsor may delegate his trial-related tasks/functions to an individual, company, institution or organization.<sup>16</sup> The Clinical Trials Regulation does not restrict the scope of such delegation and explicitly states that the delegation may concern even *all* sponsor tasks.
116. In cases where there are tasks/functions delegated the sponsor remains ultimately responsible for ensuring that the conduct of the trials and the final data generated by those trials comply with the requirements of Regulation (EU) 536/2014 as well as with those of Directive 2001/83/EC in the case of a marketing authorisation application.
117. Any trial-related tasks/functions that are delegated to a third party should be specified in writing.

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<sup>16</sup> Article 71 of Regulation (EU) No 536/2014

**5.5 Question: Does Regulation (EU) No 536/2014 establish that the sponsor, investigator, any person to whom sponsor has delegated task or his legal representative according to article 74 are liable under civil and criminal law?**

118. **Answer:** No.

119. The Clinical Trials Regulation, in referring to the “responsibility for the initiation, management and for setting up the financing of a clinical trial” (article 2(2)(14) of Clinical Trials Regulation refers to the responsibility for compliance with the Regulation.

120. Responsibility in terms of civil law (i.e. liability, for example compensation for damages occurred to a patient), or criminal law (i.e. punishment, for example criminal sanction of a bodily injury caused by negligence), is not governed by the Clinical Trials Regulation, cf. article 75. In this respect, the applicable laws of the Member States apply (see article 95 of the Regulation). Neglecting the duties or responsibilities laid out in this regulation and causing damages or bodily injury to a person can and would result in a corresponding civil and/or criminal liability according to the legal system of the respective Member State.

121. This also holds for cases where the sponsor has a legal representative in an EU Member State or EEA State. While the existence of a legal representative within the EU/EEA might be supportive to ensure effective sanctioning under national civil or criminal law, the rules for civil and criminal liability remain governed by the national laws of the Member States.

**5.6 Question: Can a sponsor established in a third country open a subsidiary or branch in a Member State in order to comply with the requirement of Regulation (EU) No 536/2014 that the sponsor or a legal representative of the sponsor must be established in the EU?**

122. **Answer:** Yes.

123. Article 74 of the Clinical Trials Regulation requires that the sponsor or, in principle, a legal representative of the sponsor is established in the EU.

124. This does not exclude the possibility that this establishment is a branch or subsidiary of a legal person having its principal seat outside the EU. This establishment could be the sponsor or act as legal representative of the sponsor established outside the EU.

**5.7 Question: What are the requirements for the legal representative of a non EEA-sponsor in view of article 74 of Regulation (EU) No 536/2014?**

125. **Answer:** If the sponsor is not established in the EU a legal representative of the sponsor has to be established in the EU.<sup>17</sup>
126. Only one legal representative can act on behalf of one sponsor in one clinical trial.
127. If the sponsor is the same for several different trials, it is acceptable (but not obligatory) to have one central legal representative in EU for all non-EU sponsored trials, as long as the responsibilities provided for by the regulation can be effectively performed
128. It is also acceptable to use an established company as a legal representative.
129. The applicant for the application to the Member State (competent authority and the Ethics Committee) might be different from the legal representative.
130. According to article 74(1) of the Clinical Trials Regulation the legal representative shall ensure compliance with the sponsor's obligations pursuant to the Regulation. This implies that the legal representative should be empowered to act on behalf of the sponsor. It also implies that the Member States may address the legal representative with any request related to the conduct of a clinical trial.
131. In order to enable the legal representative to ensure compliance with the sponsor's obligations under the Clinical Trials Regulation it is advisable that the legal representative and the sponsor conclude a contract obliging, on the one hand, the sponsor to provide the legal representative with all necessary information, and on the other hand, the legal representative to immediately notify the sponsor in case the legal representative becomes aware of any incompliance with the Regulation.
132. Member states may choose not to require the establishment of a legal representative, provided that they ensure that the sponsor establishes at least a contact person on their territory in respect of that clinical trial

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<sup>17</sup> Article 74(1) of Regulation (EU) No 536/2014.

## 6 SUBMISSION OF RESULTS OF CLINICAL TRIALS

### 6.1 Question: Which endpoints need to be summarized in the summary of results of a clinical trial?

133. **Answer:** According to article 37(4) of the Clinical Trials Regulation a summary of results needs to be submitted to the EU database within 1 year from the end of the clinical trial. The summary's content is set out in Annex IV. Point D of this Annex specified information should be provided, amongst others, on the definition and statistical analyses of endpoints. This final scientific summary should include at least results of the primary and secondary endpoints.

### 6.2 Question: Which endpoints need to be summarized in the lay summary of results of a clinical trial?

134. **Answer:** According to article 37(4) of the Clinical Trials Regulation a summary of results shall be accompanied by a summary for laypersons. The summary's content is set out in Annex V. As indicated in point 7 of the annex the overall results of the clinical trial should be given. These overall results cover the main objectives of the clinical trial and should therefore reflect at a minimum the primary endpoints, and patient relevant secondary endpoints (See also the recommendations of the expert group on clinical trials on "*Summaries of Clinical Trial Results for Laypersons*" February 2018<sup>18</sup>).

### 6.3 Question: What is a clinical trial sub-study?

135. **Answer:** A sub-study is a discrete separate study which is part of a clinical trial and should be described in the application form and in the protocol. Examples include pharmacokinetic or pharmacogenetic sub-studies.

136. Participation of clinical trial subjects in a sub-study either involves the entire trial population or a specified subgroup of subjects receiving the investigational medicinal products (IMPs) as specified in the protocol. Sub-studies should not include a trial population that is different from that of the main trial. For a sub-study an additional informed consent is required. It should be clear to subjects participating in a clinical trial if the decision to

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<sup>18</sup> [http://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017\\_01\\_26\\_summaries\\_of\\_ct\\_results\\_for\\_laypersons.pdf](http://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017_01_26_summaries_of_ct_results_for_laypersons.pdf)

take part in a sub-study is optional and separate from that of the main trial. An optional sub-study should be mentioned in the main informed consent form (ICF) and a more detailed ICF for the sub-study should be provided and signed.

#### **6.4 Question: Is the summary of results of a sub-study of a clinical trial to be reported to the EU portal?**

137. **Answer:** Sub-studies are part of the protocol and investigate a specific question in the clinical trial. Therefore results of a sub-study are expected to be available at the same time as results of the rest of the clinical trial. Therefore, a summary of results of a clinical trial including sub-studies is due within 1 year after end of the clinical trial. The plan for analysis of sub-study results should be provided within the global plan of analysis of the results of the clinical trial.
138. When additions of sub-studies occur at different time points along the clinical trial duration, the estimated dates when results for each sub-study will be available should be provided.
139. If the analysis of the results of the sub-study is going to be delayed, the sponsor has to provide a justification for it, and indicate the date when the summary of those results will be submitted. However publication of the results of a sub-study should not cause any delay in the publication of the summary of the available results of the main parts of the clinical trial.

## **7 SAFETY REPORTING**

This section is still under revision

## 8 AUTHORISATION OF MANUFACTURING AND IMPORTATION OF IMPs

### 8.1 **Question: A clinical trial with an investigational medicinal product (IMP) which is an *officinal* or *magistral* formula falls within the scope of the Clinical Trials Regulation.<sup>19</sup> What does this mean for the requirements as regards manufacturing authorisation?**

140. **Answer:** Chapter IX of the Clinical Trials Regulation applies to the manufacturing and import of the investigational medicinal product, which is subject to the holding of an authorisation. However, article 61 (5) of the Regulation provides for exceptions where an authorisation is not required under certain conditions.

141. The preparation of investigational medicinal products with an *officinal* or *magistral* formula does not require a manufacturing authorisation where this process is carried out in hospitals, health centres or clinics for exclusive use in these same places taking part in the same clinical trial in the same Member State.

142. In such cases Member States shall set up appropriate and proportionate requirements, including regular inspections, to ensure subject safety and reliability and robustness of the data generated in the clinical trial.

### 8.2 **Question: What are the regulatory requirements for the preparation of radiopharmaceuticals used as diagnostic investigational medicinal products as regards manufacturing authorisation?**

143. **Answer:** the preparation of radiopharmaceuticals used as diagnostic investigational medicinal products do not require a manufacturing authorisation where this process is carried out in hospitals, health centres or clinics for exclusive use in these same places taking part in the same clinical trial in the same Member State<sup>20</sup>.

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<sup>19</sup> Chapter IX of Regulation 536/2014

<sup>20</sup> Article 61 (5) of Regulation (EU) No 536/2014

### **8.3 Question: What are the manufacturing requirements of auxiliary medicinal products**

144. **Answer:** In order to ensure appropriate quality auxiliary medicinal products (authorised or unauthorised) should be manufactured according to the good manufacturing practice referred to in article 63(1) of Regulation (EU) No 536/2014 or to at least an equivalent standard (see also the recommendations of the expert group on clinical trials on "*Auxiliary medicinal products in clinical trials*", rev. 2, June 2017<sup>21</sup>)

### **8.4 Question: What documentation is required in the application for the authorisation of a clinical trial relating to compliance with good manufacturing practice (GMP) for an investigational medicinal product.**

145. **Answer:** The documentation required to show compliance with GMP is outlined in Annex 1 section F of the Clinical Trials Regulation:

- For products authorised in the EU (even if not manufactured in the EU) no documentation is required.
- For products with no EU authorisation or no authorisation from a country that is not a 3<sup>rd</sup> party to ICH, and not manufactured in the EU, an import authorisation and a QP declaration of GMP equivalence is required. In the latter case, if a Mutual recognition Agreement (MRA) is in place with the particular country, the latter declaration is not required if the MRA provides for this equivalence already.
- In all other cases, an import authorisation (according to article 61 of the Clinical trial Regulation) is required.

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<sup>21</sup>[https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017\\_06\\_28\\_recommendation\\_on\\_axmps.pdf](https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017_06_28_recommendation_on_axmps.pdf)

**9 “INFORMED CONSENT” AND OTHER SUBSTANTIAL REQUIREMENTS FOR CONDUCTING CLINICAL TRIALS**

**9.1 Question: What is meant by ‘compensation for participation’ in a trial involving incapacitated subjects, minors and pregnant and breast feeding women?**

146. **Answer:** according to article 31(1)(d), article 32(1)(d) and article 33(d) of the Clinical Trials Regulation no incentives or financial inducements, other than compensation for the participation in the clinical trial, are to be given to incapacitated subjects, legal representatives, minors and pregnant and breast feeding women. This compensation should not cover more than expenses and loss of earning, directly related to the participation in the clinical trials. Examples of expenses directly related to the participation in the clinical trials are travel costs for the participating subject and the legally designated representative (if applicable) or (if applicable) the person accompanying the subject, costs for accommodation, or additional costs due to participation in the clinical trial collected by the subjects’ health insurance (compulsory patient contributions/own risk). The information on compensation shall be submitted in the application dossier (Annex I, P(70)) and as such is subject to assessment by Member States. A small token of appreciation is not considered an incentive, but needs to be explicitly allowed by the ethics committee.

**9.2 Question: When can the obligation to ensure the compensation of a damage of article 76 stop?**

147. **Answer:** According to article 76 of the Clinical Trials Regulation, a clinical trial may be undertaken only if provision has been made for ensuring that a subject is compensated for any damage suffered which resulted from participation in a clinical trial. The sponsor shall make use of any appropriate arrangements existing in the Member State concerned (be it an insurance or guarantee or a similar arrangement).

148. There are no specific Union provisions on when the obligation of providing compensation for damage suffered in a clinical trial should stop.

149. However, the purpose of article 76 of the Clinical Trials Regulation is to ensure that a clinical trial subject will obtain compensation for damages caused by participating in the clinical trial independently of the financial capacity of the investigator/sponsor. Article 76 stresses also that any damage should be compensated. In view of this purpose of the provision the sponsor should ensure that the arrangements ensuring the compensation of damage are in place for the period in which such damages can arise and lawfully be claimed by the clinical trials subject.

150. The obligation to ensure the compensation of a damage proposed by the sponsor should be subject to assessment by each Member State according with national law.

**9.3 Question: What is meant by “the informed consent shall be documented” (article 29(1) of the Clinical Trials Regulation)?**

151. **Answer:** Informed consent should be written, dated and signed by the person performing the interview and by the subject or the legally designated representative in cases when the subject is unable to give informed consent. Appropriate alternative means can be used to give and record informed consent in cases when the subject is unable to write. This should be done in the presence of at least one impartial witness. Details of the process shall be recorded and the informed consent form shall be kept as evidence.

**9.4 Question: What is meant by “his or her express informed consent shall be obtained before the subject can continue to participate in the Clinical Trial” (article 32(3) of the Clinical Trials Regulation)?**

152. **Answer:** As soon as a minor participating in a clinical trial reaches the age of legal competence (as defined in national law) his/her participation in the clinical trial has to be terminated unless he/she confirms his/her consent to continue in the study by signing the informed consent form after having been properly informed in agreement with the requirements of the Clinical Trials Regulation.

## **10 START, END, TEMPORARY HALT, AND EARLY TERMINATION OF A CLINICAL TRIAL (ARTICLES 36-38 OF REGULATION (EU) No 536/2014)**

### **10.1 Question: How is the "start of a clinical trial" defined?**

153. **Answer:** Article 2 (25) of the Clinical Trials Regulation defines the "start of the clinical trial", as "*the first act of recruitment of a potential subject for a specific clinical trial, unless defined differently in the protocol*". Therefore, unless differently defined in the protocol, the date of start of the clinical trial is the date when recruitment for the clinical trial is opened in a Member State concerned. The first act of recruitment shall be identified by the sponsor in the recruitment strategy, as required per Annex I (point K.59). It could be, for example, the date of initiation of the clinical trial in the first site or the date when the first study specific advertisement is published. In some cases, the sponsor may define in the protocol the start of the trial differently than first act of recruitment. This may be justified e.g. for phase I clinical trials. However, in any case the clinical trial cannot neither start earlier than the authorisation date nor later than the first visit of the first subject.

### **10.2 Question: What should be considered as the date of the first visit of the first subject?**

154. **Answer:** The date of the first visit of the first subject should be the date the first subject or his/her legally designated representative signs his/her first informed consent to participate in activities that are protocol directed interventions.

### **10.3 Question: Which dates does the sponsor need to notify to the Member State concerned?**

155. **Answer:** The sponsor should notify each Member State concerned (MSC) of the start of a clinical trial in relation to that Member State through the EU portal, within 15 days from the start of the clinical trial in relation to that Member State.

156. Additionally, the sponsor shall notify each MSC of the first visit of the first subject in relation to that MSC through the EU portal, within 15 days from the first visit of the first subject in relation to that MSC as laid out in article 36 (1-2) of the Clinical Trials Regulation.

157. Moreover, according to article 36(3) of the Clinical Trials Regulation, the sponsor shall notify each MSC of the end of the recruitment of subjects for a clinical trial in that MSC through the EU portal, within 15 days from the end of the recruitment of subjects. In cases when recruitment is re-started

sponsors should notify MSC through the portal within 15 days of the re-start in each MSC (see also Q10.4).

#### **10.4 Question: How is "temporary halt of a clinical trial" defined**

158. **Answer:** Article 2 (28) of the Clinical Trials Regulation defines the "temporary halt of a clinical trial" as an "interruption not provided in the protocol of the conduct of a clinical trial by the sponsor with the intention of sponsor to resume it." This could also be part of an urgent safety measure (article 54 of the Clinical Trials Regulation).
159. A temporary halt implies that the sponsor makes unforeseen stops of any clinical trial (CT) activity described in the protocol (i.e. recruitment only or recruitment and treatment), due to unexpected circumstances that could affect the benefit/risk ratio or not. In case of safety issues subjects need to be monitored/followed up. During the temporary halt the issues of concern are assessed together with the need for possible changes in the CT. After this analysis is completed, and reassurance that any potential problem may be solved or mitigated, the sponsor could either restart or end the CT.
160. In case the reasons for the temporary halt have the potential to affect the benefit/risk balance (i.e. concern related to safety, lack of efficacy or IMP quality defect), the sponsor should request a restart of the CT through a substantial modification subject to authorisation, providing the justification for the restart, including conclusions of the analysis, the mitigation measures if applicable and an updated benefit/risk assessment.
161. When the reasons for a temporary halt have had no potential effect on the benefit/risk balance (e.g. lack of supply of IMP/shortages), the sponsor should notify when the CT is resumed within 15 days of the restart of the CT.
162. If a temporarily halted CT is not resumed within two years, the expiry date of this period or the date of the decision of the sponsor not to resume the clinical trial, whichever is earlier, shall be deemed to be the date of the end of the CT. In the case of early termination of the CT, the date of the early termination shall be deemed to be the date of the end of the CT.

#### **10.5 Question: If a clinical trial temporarily halted according to articles 37 and 38 is not resumed within two years, can the re-start date of the clinical trial occur after the two-year period?**

163. **Answer:** Sponsors need to submit a substantial modification (SM) to restart a clinical trial (CT) halted for reasons of subject safety (article 38(2) of the Clinical Trials Regulation). However in case a sponsor intends to restart a CT halted for reasons other than subject safety within the 2-year period

from the date of the temporary halt, he shall notify this to each Member State concerned through the EU portal.

164. A sponsor can submit within the two-year period following a temporary halt a SM requesting a restart date **after** the 2-year period. This SM can only be submitted **before** the expiry of the 2-year period and applies to temporary halts for reasons of subject safety or not.

**10.6 Question: If a clinical trial temporarily halted according to article 38 is not resumed within two years, will article 37(7) also apply?**

165. **Answer:** In case of clinical trials that are temporary halted for reasons of subject safety (article 38: change of benefit-risk balance) sponsors are encouraged to notify the Member States concerned any follow up that has been taken or that is needed, **before** the 2-year expiry.

**10.7 Question: How should urgent safety measures (article 54) involving temporary halts (articles 38) be notified?**

166. **Answer:** Urgent safety measures may involve a temporary halt of the clinical trial due to safety reasons. In such cases, notification of the temporary halt and of the urgent safety measure should be made without undue delay but no later than seven days for the notification of an urgent safety measure (article 54 of the Clinical Trials Regulation) and 15 days for a temporary halt (article 38 of the Clinical Trials Regulation).

**10.8 Question: Would a halt of recruitment be considered as a temporary halt of a clinical trial or of an end of recruitment?**

167. **Answer:** If the recruitment is stopped due to a potential change in the benefit-risk balance (e.g a safety related issue), this should be notified as a temporary halt of the clinical trial. The sponsor should notify the Member States concerned without undue delay but not later than 15 days, including reasons for such action and specify follow up (article 38 of the Clinical Trials Regulation). An additional change of benefit-risk notification or an urgent safety measure may need to be submitted. The sponsor should apply for a substantial modification before re-starting the clinical trial (article 38 of the Clinical Trials Regulation) (see also Q10.4).
168. However, if the recruitment is halted due to problems of reaching potential subjects for participation in the clinical trial, this should be notified as an end of recruitment. The sponsor can then decide to restart the recruitment, and notify it according to article 36(3) of the Clinical Trials Regulation (see also Q10.3).

**10.9 Question: How is "suspension of a clinical trial" defined?**

169. **Answer:** Article 2(29) of the Clinical Trials Regulation defines suspension of a clinical trial as "interruption of the conduct of a clinical trial by a Member State". This can be decided by the Member State concerned when taking a corrective measure, as defined in article 77, on the grounds that the clinical trial does not meet the requirements set out in the Clinical Trials Regulation.

**10.10 Question: How is "early termination" defined?**

170. **Answer:** Article 2(27) of Clinical Trials Regulation defines early termination as "the premature end of a clinical trial due to any reason before the conditions specified in the protocol are complied with".

171. In the case of early termination of a clinical trial (CT) for reasons not affecting the benefit-risk balance, such as low recruitment, drug supply, end of development, the sponsor shall notify each Member State concerned through the EU portal of the reasons for such action and, when appropriate, follow-up measures for the subjects.

172. An earlier end of a CT which is not based on grounds of safety, but on other grounds, such as faster recruitment than anticipated, may not be considered as "early termination".

173. There may be cases where a CT is ended earlier for reasons of lack of efficacy. This would impact the benefit-risk balance and is to be understood as a safety issue. In such cases, the early termination should be notified without undue delay but not later than 15 days and shall include reasons for such action and specify follow-up measures (article 38 of the Clinical Trials Regulation).

**10.11 Question: If no subject has been included in a clinical trial in a Member State concerned, how should a sponsor proceed?**

174. **Answer:** the necessary measures depend on the situation.

175. If no subject has been included in a clinical trial (CT) in a Member State concerned (MSC) this means that the first visit of the first subject did not take place and therefore the subject did not sign an informed consent to participate in activities that are protocol directed interventions (see also Q10.2).

176. The first act of recruitment, as defined in the protocol (e.g. publication of an advertisement for recruitment), may have occurred and therefore the CT may have started (see Q10.1). However if no subject was subsequently included due to, for example, unsuccessful recruitment, the authorisation for

this MSC will expire within 2 years from the date of authorisation (article 8(9) of the Clinical Trials Regulation). This expiration will be tacit and therefore it is important that sponsors do report the first visit of the first subject before the expiration date.

177. In a situation where no subject was included a sponsor may:

- notify early termination of the CT in the MSC (article 2(27) and article 37 of the Clinical Trials Regulation) (see Q10.10);
- submit a substantial modification according to Chapter III of the Clinical Trials Regulation within two years from the decision on the CT to include further sites;
- submit a substantial modification according to Chapter III of the Clinical Trials Regulation to ask for an extension of the authorisation, including a justification clarifying the feasibility of the CT. If an extension was not submitted and approved within two years from the decision on the clinical trial, the authorisation shall expire in that MSC. The sponsor will then have to submit a new application as per article 14 of the Clinical Trials Regulation.

178. If no subject is included in a CT in *only one of several sites* in a MSC the CT can, in principle, continue. However, scientifically, the sponsor should assess the potential impact on the overall recruitment. Additionally a substantial modification may be required (e.g. to add another site, or extend the recruitment period for other sites).

### **10.12 Question: How is “end of a clinical trial” defined? What are the sponsor's obligations after the clinical trial ends?**

179. **Answer:** Article 2(26) of the clinical trial Regulation defines "end of a clinical trial" as "the last visit of the last subject, or at a later point in time as defined in the protocol".

180. The sponsor shall notify each Member State concerned (MSC) in the EU/EEA of the end of a clinical trial (CT) **in relation to that MSC** through the EU portal, within 15 days from the end of the CT in relation to that MSC.

181. Additionally the sponsor shall notify each MSC of the end of a CT **in all MSC in the EU/EEA as well as in all third countries** through the EU portal, within 15 days from the end of the CT in the last of the MSC as well as in the last of the MSC and third countries in which the CT has been conducted.

182. Irrespective of the outcome of a CT, within one year from the end of the CT in all MSC in the EU/EEA (and from not the global end of the CT. See

article 37(4), recital 39 and point 184 below), the sponsor shall submit to the EU database:

- a summary of the results of the CT, in line with Annex IV of the Clinical Trials Regulation.
  - a summary for laypersons, in line with Annex V of the Clinical Trials Regulation.
183. In cases where the CT was intended to be used for obtaining a marketing authorisation for the investigational medicinal product a clinical study report should be submitted to the EU database by the applicant for marketing authorisation within 30 days after the day the marketing authorisation has been granted, the procedure for granting the marketing authorisation has been completed, or the applicant for marketing authorisation has withdrawn the application.
184. Where, for scientific reasons detailed in the protocol, it is not possible to submit a summary of the results within one year, for example when the clinical trial is still ongoing in third countries and data from that part of the trial are not available, which makes a statistical analysis not relevant, the summary of results shall be submitted as soon as it is available. In this case, the protocol shall specify when the results are going to be submitted, together with a justification (see article 37(4) and Recital 39 of the Clinical Trials Regulation).

## 11 ARRANGEMENTS FOR THE TRANSITIONAL PERIOD

### 11.1 **Question: What will happen to those clinical trials that started prior to the date of entry into application of Directive 2001/20/EC and that have not been aligned with the requirements of the Directive?**

185. **Answer:** Those clinical trials do not benefit from the transitional provisions of the Regulation. As a consequence, those trials cannot continue after the entry into application of the Clinical Trials Regulation. The sponsor should assess whether those trials are interventional or merely observational. In case the trial is still to be considered as interventional and it is impossible to terminate a trial for reasons related to patient safety or scientific soundness, a sponsor should apply for a new authorisation of that trial under the Clinical Trials Regulation.

### 11.2 **Question: At what point in time should the regulatory framework of a clinical trial switch from the Clinical Trials Directive to the Clinical Trials Regulation?**

186. **Answer:** The possibility to switch the regulatory framework under which a clinical trial is conducted from the Directive to the Regulation should be **open from the day of the entry into application of the Regulation till the end of the 3-year transitional period**, without the need to discontinue a clinical trial or put a trial on hold.

187. The sponsors should however take into account the time necessary for completion of the authorisation procedure under the Clinical Trials Regulation (at maximum 60 days) and submit the application early enough before the end of the transitional period.

### 11.3 **Question: What are the conditions for switching the regulatory framework of a trial from the clinical trials Directive to the Clinical Trials Regulation?**

188. **Answer:** Only clinical trials that comply with the Clinical Trials Regulation as regards **their substantial requirements** can benefit from the proposed solution. It is the **sponsor's responsibility** to assess this compliance. 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 Regulation, does not comply with the said Regulation.

189. Moreover, only active clinical trials without any pending/ongoing assessment in any of the EU/EEA countries are eligible for a switch of the regulatory regime (therefore e.g. clinical trials that are temporary halted or trials for which a request for a substantial amendment was submitted would not be eligible to be transitioned until the procedure/s is completed).

#### **11.4 Question: What if a clinical trial does not comply with the Clinical Trials Regulation?**

190. **Answer:** If a trial **does not comply** with the Clinical Trials Regulation, a sponsor shall **request a substantial amendment under the clinical trials Directive** before switching to the regulatory framework of the Regulation, specifying its intention to align the trial with the Regulation. Only after the substantial amendment is accepted, a sponsor can follow the procedures described below to switch the clinical trial to the regulatory framework of the Regulation.

#### **11.5 Question: How can a sponsor switch a clinical trial to the regulatory framework of the Clinical Trials Regulation?**

191. **Answer:** The sponsor shall submit an initial application (article 5 of the Clinical Trials Regulation) to the EU Portal and Database (EUPD) but relying, in 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 EUPD**, and in case of multinational clinical trials, **a harmonised or at least a consolidated protocol** (see: *CTFG Best Practice Guide for sponsors of multinational clinical trials with different protocol versions approved in different Member States under Directive 2001/20/EC that will transition to Regulation (EU) No 536/2014*<sup>22</sup>). The trial will fall under the regulatory framework of the Regulation as of the tacit approval date (60 days from the submission).

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<sup>22</sup> <http://www.hma.eu/ctfg.html>

## 11.6 Question: How shall a sponsor proceed in case of mono-national clinical trials?

192. **Answer:** In case of **mono-national trials** a protocol is authorised under the Directive only in one Member State. Sponsors will need to upload, in addition to the new cover letter and new application form (Part I and II), the following information as regards Part I:

- the latest approved version of the protocol (as authorised by the Member State in question);
- IB,
- GMP relevant documents;
- IMPD;
- The existing documents related to auxiliary medicinal products, as submitted for the assessment in the context of the initial application (if applicable).

193. The documents required to be uploaded as regards Part II are the subjects' information sheet, the informed consent form and information on the informed consent procedure and the ethics committee opinion that was issued as part of the authorisation of the clinical trial. In case the sponsor cannot provide certain documents listed in Annex I of the Regulation, and not required under Directive, the sponsor should upload a blank document clarifying that this aspect was assessed by National Competent Authority (NCA) and/or Research Ethics Committee (REC) and therefore is covered by the conclusion of the assessment.

## 11.7 Question: How should a sponsor proceed in case of multinational clinical trials?

194. **Answer:** A **multinational clinical trial** is a trial conducted in different Member States under the **same EudraCT number**. A multinational trial that is fully or sufficiently harmonised, - that is, the protocols of the trials conducted in the different Member States under the same EudraCT number are the same, or nearly the same - can benefit from the below proposed solution, on the condition that they comply with the Clinical Trials Regulation.

195. For trials that are not fully, but sufficiently harmonised, a sponsor needs to prepare a **consolidated protocol** (reflecting the common core provisions and capturing the minor differences as regards the nationally authorised

trials (please see *CTFG Best Practice Guide for sponsors of multinational clinical trials with different protocol versions approved in different Member States under Directive 2001/20/EC that will transition to Regulation (EU) No. 536/2014*<sup>23</sup>). The consolidated protocol **must correspond to what is authorised in each of the Member States** concerned. As such, a consolidated protocol does not require a substantial amendment, if it properly reflects the scope and conditions of the authorisation of the clinical trial in each of the Member State concerned and complies with the Clinical Trials Regulation. It is the sponsor's responsibility to ensure that a consolidated protocol reflects what is authorised in each of the Member States.

196. For clinical trials in the Voluntary Harmonisation Procedure (VHP), the Member State of the VHP Reference National Competent Authority (Ref-NCA) shall be indicated as the Reporting Member State. This applies also to trials that are partly in the VHP. For multinational clinical trials that are outside the VHP, a sponsor will propose the Reporting Member State (RMS) in the application form submitted with the required documents. The RMS will then be selected by the Member States Concerned in accordance with the rules established under the Regulation.
197. In order to switch the regulatory framework applicable to a multinational trial from the Directive to the Regulation, the sponsor will need to apply following the workflow of an initial application (article 5 of the Regulation), and submit the following information as regards Part I:
  - New cover letter;
  - New application form (Part I and Part II);
  - Consolidated protocol;
  - IB,
  - GMP relevant documents;
  - IMPD;
  - The existing documents related to auxiliary medicinal products, submitted for the assessment in the context of the initial application (if applicable).
198. The documents required to be uploaded as regards Part II are the subjects' information sheet, the informed consent form and information on the informed consent procedure and the ethics committee opinion issued as part of the authorisation of the trial. In case the sponsor cannot provide certain documents listed in Annex I of the Regulation, and not required under

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<sup>23</sup> <http://www.hma.eu/ctfg.html>

Directive, a sponsor should upload a blank document clarifying that this aspect was assessed by National Competent Authority (NCA) and/or Research Ethics Committee (REC) and therefore is covered by the conclusion of the assessment.

**11.8 Question: What if a multinational clinical trial (conducted under the same EudraCT number in different Member States) is not sufficiently harmonised?**

199. **Answer:** If clinical trials conducted under the same EudraCT number in different Member States are not sufficiently harmonised, a sponsor needs to harmonise them via substantial amendments under Directive 2001/20/EC in order to be able to switch them as one trial under the Clinical Trials Regulation. The process of aligning the trials can begin before the Regulation applies and should end within sufficient time before the end of the transitional period, taking into account the time necessary for an authorisation procedure under the Regulation.

**11.9 Question: What will happen with the clinical trials included in the Voluntary Harmonisation Procedure (VHP)?**

200. **Answer:** The Voluntary Harmonisation Procedure (VHP) will discontinue as of entry into application of the clinical trials Regulation. The clinical trials included in the VHP will, in principle, qualify to transition as multinational clinical trials (see Q11.7). It is the sponsor's responsibility to assess however whether this is the case (as described in this document) and, in case a harmonised protocol does not exist, to prepare one consolidated protocol reflecting acceptable differences in authorised national trials (please see *CTFG Best Practice Guide for sponsors of multinational clinical trials with different protocol versions approved in different Member States under Directive 2001/20/EC that will transition to Regulation (EU) No. 536/2014*<sup>24</sup>). In order to benefit from the advantages of harmonisation a sponsor should transition those trials as soon as possible after the entry into application of the Regulation, and at the latest before any new submission concerning a trial.

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<sup>24</sup> <http://www.hma.eu/ctfg.html>

**11.10 Question: What are the consequences of switching the regulatory framework applicable to a clinical trial?**

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

**11.11 Question: When is a sponsor expected to complete the application dossier, in line with Annex I of the Clinical Trials Regulation?**

202. **Answer:** At the moment of the first application submitted after the a clinical trial has transitioned and therefore submitted under the rules of the Regulation (i.e. the next substantial modification or addition of a new Member State) the sponsor should, in principle, **complete the application dossier** in accordance with the requirements of Annex I of the Regulation, at least with regard to that part of the application dossier which will be assessed in the procedure (e.g. in case of a substantial modification on Part II only, a sponsor should complete all elements related to Part II of the dossier relevant for the Member State(s) concerned by the substantial modification).

**11.12 Question: What should a sponsor do in case an urgent substantial modification is required after the submission of the application for transitioning a clinical trial to the Clinical trials Regulation?**

203. **Answer:** A sponsor should take necessary measures and inform the Reporting Member State (RMS) and other Member States concerned. A RMS may decide to speed up the transitioning procedure to allow a sponsor to introduce a request for a substantial modification under the Regulation. The RMS may also advise the sponsor to withdraw the request for transitioning the trial and submit the request for substantial amendment under the clinical trials Directive. The sponsor can then resubmit the request for transitioning the trial once the decision on the substantial amendment is issued.

**11.13 Question: What are the applicable transparency requirements?**

204. **Answer:** Documents submitted by the sponsor in the application dossier for the transition of a clinical trial to the Clinical Trials Regulation will fall under the transparency requirements, as any other application dossier, and will be made publicly available.

205. The documents issued under the clinical trials Directive, which were not destined to be made public initially, will not fall retroactively under the transparency requirements (e.g. inspection reports, notifications).
206. Any new document produced as of the moment of the transition of a trial will fully fall under the transparency rules of the Clinical Trials Regulation (the transparency rules applicable to the Portal will apply to them, including deferrals for making certain documents publicly available).
207. Clinical trials that were initially started under the Directive and switched to the Regulation have to comply with all the obligations of the Regulation e.g. the publication of summary of results, notifications and, if applicable, the Clinical Study Report (CSR).

## 12 MISCELLANEOUS

### 12.1 Question: Can the reporting Member State be changed?

208. **Answer:** The Clinical Trials Regulation does not provide for a procedure to change the reporting Member State. The Regulation actually specifies in articles 14(2) and 17(1) that the reporting Member State for an initial authorisation procedure will be the reporting Member State for the authorisation of an additional Member State or for a substantial modification.
209. Therefore in case a clinical trial is not on-going in a reporting Member State (due to e.g. a withdrawn or lapsed application) it is not possible to change the reporting Member State.
210. However, it may be possible for a reporting Member State to delegate/contract out the work to another Member State concerned but the responsibility will still lie with the original reporting Member State, who assessed the original application, and should continue to assess any follow ups or substantial modifications under the same criteria.

### 12.2 Question: Can a corrective measure be taken by a Member State after the end of a clinical trial?

211. **Answer:** Corrective measures referred to in article 77 of the Clinical Trials Regulation are expected to be taken in the majority of cases by Member States while a clinical trial is on-going. However when follow up of patients for safety reasons is deemed necessary Member States may decide to take a corrective measure after a clinical trial has ended and apply article 77(1)(c).

## **Annex I      Examples of substantial and non-substantial modifications**

**The following are non-exhaustive lists of examples of substantial and non-substantial modifications that serve as guidance for a case-by-case decision of the sponsor. Please see Q3.2 on what is understood by the notion of substantial.**

It is important to note that certain substantial modifications may lead to changes in the clinical trial to an extent that it has to be considered to be a completely new clinical trial. In such cases an application for a new trial authorisation would be required. For examples see Q3.2.

### **Part I**

#### **a. Modifications that are typically considered to be ‘substantial’:**

*Note: Modifications marked with \* may be considered to lead to a completely new clinical trial unless justified.*

#### *Protocol*

1. Change of secondary endpoint which is likely to have a significant impact on the safety or scientific value of the clinical trial<sup>25\*</sup>;
  2. Use of a new mode of measurement for the primary endpoint\*;
  3. New toxicological or pharmacological data or new interpretation of toxicological or pharmacological data which is likely to impact on the risk/benefit assessment;
  4. A change in the definition of the end of the trial;
  5. Removal of a trial arm not foreseen in the approved protocol;
  6. change of inclusion or exclusion criteria if these changes are likely to have a significant impact on the safety or scientific value of the clinical trial\*;
  7. Changes in the number of scheduled subject study visits;
  8. Change of a diagnostic or medical monitoring procedure which is likely to have a significant impact on the safety or scientific value of the clinical trial;
  9. Removal of an independent data monitoring board;
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10. Change of treatment modalities (mode of administration/duration/frequency/dosing) of IMPs;
11. A change of study design which is likely to have a significant impact on primary or major secondary statistical analysis or the risk/benefit assessment\*;
12. Amending the number of subjects to be included, either due to an adaptation of the sample size calculation or to maintain a previously defined sample size calculation due to more withdrawals/drop outs than expected;
13. Addition of an interim/intermediate analysis. No interim analysis was mentioned and specified in the initial protocol but during the study it is decided to do an interim analysis;
14. Deletion of an interim/intermediate analysis;
15. Additional safety monitoring and/or other type of changes in order to minimize a potential safety concern;
16. Change of safety criteria to modify or interrupt IMPs treatment.

*IMPD and IB*

17. Any change in the quality of the IMP (see also the relevant EMA guidelines);<sup>26</sup>
18. Change in the overall risk and benefit assessment in the IMPD or IB;
19. New toxicological or pharmacological data or new interpretation of the data in the IMPD or IB which might have a significant impact on the risk/benefit ratio;
20. New clinical data e.g. from previous clinical trials and human experience in the IMPD or IB which might have a significant impact on the risk/benefit ratio;

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<sup>26</sup> With regard to changes in the IMPD, guidance is contained in Chapter 9 of the Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials – Revision 1 EMA/CHMP/QWP/545525/2017 which is available here: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/document/document\\_detail.jsp?webContentId=WC500239381&mid=WC0b01ac058009a3dc](http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500239381&mid=WC0b01ac058009a3dc)

Also refer to Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials - EMA/CHMP/BWP/534898/2008 rev. 1 which is available here: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/document/document\\_detail.jsp?webContentId=WC500237742&mid=WC0b01ac058009a3dc](http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500237742&mid=WC0b01ac058009a3dc)

21. Changes to the reference safety information for the annual safety report and SUSAR reporting;

*Other modifications*

22. A change of sponsor, co-sponsor or the sponsor's legal representative;
23. The revocation or suspension of the IMP's marketing authorisation.

**b. Modifications that are typically considered not to be 'substantial':**

*Protocol*

1. The addition/deletion of exploratory/tertiary endpoints;
2. An increase in duration of the overall time of the trial, provided that the following conditions are met:
  - i. the exposure to treatment with the IMP is not extended;
  - ii. the definition of the end of the trial is unchanged; and
  - iii. scheduled subject study visits arrangements are unchanged;

If there is a change in one or more of these conditions, it would be considered to be a substantial modification.

3. A change in the number of clinical trial participants per trial site, if the total number of participants in the Member State concerned is identical or the increase/decrease is insignificant (i.e. not related to a change in sample size calculation) in view of the absolute number of participants;
4. A change in the number of clinical trial participants in the Member State concerned, if the total number of participants is identical or the increase/decrease is insignificant (i.e. not related to a change in sample size calculation) in view of the absolute number of participants;
5. A change in the documentation used by the research team for recording study data (e.g. case report form or data collection form);

*General*

6. Correction of typographical errors in any document.

***c. Non substantial modifications that the sponsor should notify within the EU Portal and database.***

*Note: As provided for in the Clinical Trials Regulation changes which are not substantial modifications but are relevant for the supervision of the clinical trial by the Member States concerned should be updated in the EU portal and database. Below is a non-exhaustive list of changes related to Part I that sponsors should notify in the portal:*

1. In accordance with article 55 of Regulation (EU) no 536/2014 the sponsor should review the Investigator's Brochure at least annually. The sponsor has to verify whether the update relates to changes which are to be considered as substantial e.g. new information relevant for benefit or risk assessment and analysis, update of reference safety information etc. In such cases, the rules for notification of substantial modifications would apply. If the update does not include substantial modifications, it should be submitted as a non-substantial modification in the clinical trial portal;
2. Any change of persons/entities and contact details to whom the sponsor delegated tasks for example the applicant, technical service providers, electronic systems providers, laboratories and clinical research organisations ('CROs') (note: Such changes related to the sponsor, his legal representative/contact persons, or the principal investigator are considered to be a substantial modification. Additionally the responsibility *vis-à-vis* the Member State for a clinical trial is always with the sponsor or his legal representative/contact person);
3. Changes regarding which co-sponsor is responsible for the tasks referred to in article 72(2) of the Clinical Trial Regulation.

**Part II**

***a. Modifications that are typically considered to be 'substantial'***

1. Addition of a site, change in facilities, change in site suitability or change of principal investigator;
2. New insurance policy;
3. Change in the insurance policy, eg. a new insurance company, changes in insurance coverage, conditions and/or insured amounts;
4. Modifications in any documents for subjects such as the subject information sheet, and informed consent form, which could include change in safety information, study procedures or data handling;
5. Change in access, disclosure, dissemination, alteration or loss of information and personal data processed;
6. Change in collection, storage and future use of biological samples from clinical trial subject;

7. Change in financial arrangements;
8. Change in the compensation paid to subjects and/or investigator/site for participating in the trial;
9. Change in recruitment arrangements including procedures for inclusion of subjects and advertising material.

***b. Modifications that are typically deemed not to be substantial***

1. Extension of validity of insurance certificate;
2. Correction of typos in any document.

***c. Non substantial modifications that the sponsor should notify within the EU Portal and database.***

*Note: As provided for in the Clinical Trials Regulation changes which are not substantial modifications but are relevant for the supervision of the clinical trial by the Member States concerned should be updated in the EU portal and database. Below is a non-exhaustive list of changes related to Part II that sponsors should notify in the portal:*

1. The closure of an approved trial site;
2. Technical and administrative changes in subject documents including the subject information sheet or informed consent eg change in phone number or typo errors;
3. A validated translation of the local approved ICF in another language in order to be used for a potential subject who is not fluent in the local (country) language;

## Annex II: Decision tree to establish a whether a trial is a “clinical trial”

**Note:** this Annex is still under discussion in the expert group on clinical trials

This algorithm and its endnotes will help you answer that question. Please start in column A and follow the instructions. Additional information is provided in the notes at the end of the table. If you have doubts about the answer to any of the questions contact the clinical trials unit of your competent authority.

	A	B	C	D	E	F
<b>A CLINICAL TRIAL OF A MEDICINAL PRODUCT?</b>					<b>A NON-INTERVENTIONAL STUDY?</b>	<b>A LOW-INTERVENTION CLINICAL TRIAL?</b>
Is a medicinal product administered before or during the start of the clinical trial	Is it a medicinal product (MP)? <sup>1</sup>	Is it not a medicinal product?	What effects of the medicine are you looking for?	Why are you looking for those effects?	How are you looking for those effects?	Is the product authorised in any EU Member State?
<p>If a medicinal product is administered before the start of the clinical trial, and it falls under current practice, please go to column E.</p> <p>If a medicinal product is administered before the start of the clinical trial and it falls not under current practice, column E is excluded.</p> <p>If a medicinal product is administered after the start of the clinical trial, please go to column A.</p>	<p>If you answer no to <u>all</u> the questions in column A, the activity is not a clinical trial on a MP.</p> <p>If you answer yes to <u>any</u> of the questions below go to column B.</p>	<p>If you answer yes to the question below in column B the activity is not a clinical trial on a MP.</p> <p>If you answer no to this question below go to column C.</p>	<p>If you answer no to <u>all</u> the questions in column C the activity is not a clinical trial under the scope of Regulation EU No 536/2014.</p> <p>If you answer yes to <u>any</u> of the questions below go to column D.</p>	<p>If you answer no to <u>all</u> the questions in column D the activity is not a clinical trial under the scope of Regulation EU No 536/2014.</p> <p>If you answer yes to <u>any</u> of the questions below go to column E.</p>	<p>If you answer NO to <u>all</u> these questions the activity is a non-interventional trial which is outside the scope of Regulation EU No 536/2014.</p> <p>If your answers in columns A,B,C &amp; D brought you to column E and you answer YES to <u>any</u> of these questions the activity is a clinical trial within the scope of the Regulation.</p>	<p>If your answer in column E is YES, and you answer NO to any of the questions below, the activity is a clinical trial within the scope of Regulation EU No 536/2014 but is NOT a low-intervention clinical trial as defined in the Regulation.</p> <p>If your answer in column E is YES, and if you answer YES to ALL of the questions below, the activity is a low-intervention clinical trial as defined by the Regulation.</p>

	<p>A.1. Is it a substance<sup>ii</sup> or combination of substances presented as having properties for treating or preventing disease in human beings?</p> <p>A.2. Does the substance function as a medicine? i.e. can it be administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action or to making a medical diagnosis or is otherwise administered for a medicinal purpose?</p> <p>A.3. Is it an active substance in a pharmaceutical form?</p>	<p>B.1. Are you <u>only</u> administering any of the following substances?</p> <ul style="list-style-type: none"> <li>• Human whole blood<sup>iii</sup>;</li> <li>• Human blood cells;</li> <li>• Human plasma;</li> <li>• A food product<sup>iv</sup> (including dietary supplements) not presented as a medicine;</li> <li>• A cosmetic product<sup>v</sup></li> <li>• A medical device</li> </ul>	<p>C.1. To discover or verify/compare its clinical effects?</p> <p>C.2. To discover or verify/compare its pharmacological effects, e.g. pharmacodynamics?</p> <p>C.3. To identify or verify/compare its adverse reactions?</p> <p>C.4. To study or verify/compare its pharmacokinetics, e.g., absorption, distribution, metabolism or excretion?</p>	<p>D.1. To ascertain or verify/compare the efficacy<sup>vi</sup> of the medicine?</p> <p>D.2. To ascertain or verify/compare the safety of the medicine?</p>	<p>E.1. Does the assignment of any patient involved in the study to a particular therapeutic strategy decided in advance by a clinical trial protocol<sup>vii</sup> and does not fall within current practice?</p> <p>E.2. Is the decision to prescribe a particular medicinal product clearly taken together with the decision to include the patient in the study?</p> <p>E.3. Will diagnostic or monitoring procedures be applied to the patients included in the study, other than those which are applied in the course of current practice related to the condition?</p>	<p>F.1. Is this a study of one or more medicinal products, which have a marketing authorisation in the Member State concerned?</p> <p>F.2. Does the protocol of the clinical trial specify that (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;</p> <p>F.3. Do the additional diagnostic or monitoring procedures 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?</p>
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<sup>i</sup> Cf. Article 1(2) of Directive 2001/83/EC, as amended

<sup>ii</sup> Substance is any matter irrespective of origin e.g. human, animal, vegetable or chemical that is being administered to a human being.

<sup>iii</sup> This does not include derivatives of human whole blood, human blood cells and human plasma that involve a manufacturing process.

<sup>iv</sup> Any ingested product which is not a medicine is regarded as a food. A food is unlikely to be classified as a medicine unless it contains one or more ingredients generally regarded as medicinal and indicative of a medicinal purpose.

<sup>v</sup> The Cosmetic Directive 76/768/EC, as amended harmonises the requirements for cosmetics in the European Community. A "cosmetic product" means any substance or preparation intended for placing in contact with the various external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and mucous membranes of the oral cavity with the view exclusively or principally to cleaning them, perfuming them or protecting them in order to keep them in good condition, change their appearance or correct body odours.

<sup>vi</sup> Efficacy is the concept of demonstrating scientifically whether and to what extent a medicine is capable of diagnosing, preventing or treating a disease and derives from EU pharmaceutical legislation.

<sup>vii</sup> Assignment of patients to a treatment group by randomisation planned by a clinical trial protocol cannot be considered as current practice.