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CLINICAL TRIALS REGULATION (EU) NO 536/2014

DRAFT

QUESTIONS & ANSWERS

VERSION 4

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.

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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. This document aims at informing on the technical aspects of Commission Clinical Trials Regulation (EU) No 356/2014 with a view to facilitating its implementation.

This documents sets out frequently-asked 'questions and answers' regarding the implementation of the rules on clinical trials. All updates to this questions and answers document are presented and discussed within the "Expert group on 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.

Chapter 7 on "Safety Reporting" was drafted by the Clinical Trials Facilitation and Coordination Group of the Heads of Medicines Agency (CTFG) and endorsed by the Expert Group on Clinical Trials of the European Commission.

Q&A 2.8 "How to use conditions" was endorsed also by CTFG.

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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?

7. **Answer:** The new Clinical Trials legislation has taken the legal form of a Regulation[1] 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.

8. 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

9. 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;
- 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;

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

- 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?

10. **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”?

11. **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 I 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"?

12. **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;

13. The decision tree in Annex I 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"?

14. **Answer:** According to Article 1 of the Clinical Trials Regulation, non-interventional studies are excluded from the scope of this Regulation.

15. 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".

16. 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.

17. The decision tree in Annex I can be used to identify whether a trial is a non-intervention clinical trial in the sense of Regulation (EU) No 536/2014.

18. 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.

19. Moreover, this restriction shall ensure that medical activities which are normal clinical practice (see also Q&A 1.18) 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?

20. Answer: Yes.

21. 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 I).

22. '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."

23. 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.

24. 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;[2] and
- Medicinal product – medical device[3]

[2] Available here: https://ec.europa.eu/growth/sectors/cosmetics/products/borderline-products_en

[3] Available here : https://ec.europa.eu/growth/sectors/medical-devices/guidance_en

- Medicinal product - food supplements[4]

25. 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.

26. This includes also medicinal products which are specifically addressed in the EU law on pharmaceuticals, such as advanced therapy medicinal products[5], or medicinal products derived from human blood or human plasma as defined in Article 1(10) of Directive 2001/83/EC. It is important to keep in mind that specific guidance[6] exists on the classification of a medicinal product as an advanced therapy medicinal product for marketing authorization applications.

27. 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.

28. 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[7].

29. The classification of a substance as a medicinal product is the sole responsibility of the member states. Sponsors should seek advice at the level of the member states concerned if the status of a research product is unclear.

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4 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

5 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).

6 Available here : https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-classification-advanced-therapy-medicinal-products_en-0.pdf

7 cf., for example, http://ec.europa.eu/growth/sectors/cosmetics/products/borderline-products/index_en.htm

1.7 Question: What is not considered as "normal clinical practice"?

30. For the classification as a clinical trial vs. a non-interventional study the assignment to one of the following therapeutic strategies is NOT considered „normal clinical practice" as defined by Article 2 (6) of Regulation (EU) 536/2014:

- Administration of a medicinal product without a marketing authorisation in the EEA[8].
- Administration of a medicinal product in healthy volunteers or in patients without clinical indication or medical need.
- Other unproven interventions as defined in Article 37 of the Declaration of Helsinki.
- Blinding or randomisation of treatment allocation.
- Additional or more frequent/increased diagnostic or monitoring procedures or sampling performed solely for the purposes of the clinical study.
- Any procedures not considered clinical practice for the individual patient within the framework of the National Healthcare System of the Member State concerned with the clinical study.

31. With regard to off-label use of medicinal products with a marketing authorisation in the EEA it is within the competence of each Member State to determine if established off-label use in principle is considered within their normal clinical practice and can be investigated in a non-interventional study or not.

32. Sponsors are recommended at the planning stage of such a clinical study/clinical trial to seek advice from all Member States where the study/trial is intended to take place. A clinical trial application should then be submitted to all Member States where the conduct of a non-interventional study is not possible.

1.8 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?

33. Answer: No.

34. There may be studies, which have the only objective to investigate the physiology of the body. In these investigations the medicinal product is used as *a tool* with the aim to provoke a *well characterized physiological response* in humans. These studies

[8] The systematic investigation of medicinal products where no marketing authorization is foreseen, e.g. magisterial formulations, is restricted to clinical trials

should not address the diagnostic, prophylactic or therapeutic potential of the medicinal product nor its pharmacokinetic or pharmacodynamic profile. For medicinal products that do not have marketing authorisation, the *desired pharmacological response should be corroborated by published scientific evidence in humans on safety and efficacy supporting the chosen dose level and route of administration*. 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).

35. 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.

36. 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.

37. 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).

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

38. **Answer**: A radiopharmaceutical used as diagnostic agent in a positron emission tomography (PET) study is a medicinal product.

39. 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).

40. 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.

41. 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.

[redacted]

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

46. **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.

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

47. **Answer**: Yes. The 'hospital exemption' for advanced therapy medicinal products, which is contained in article 3(7) of the Directive 2001/83/EC 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).

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

48. **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*".

49. Comparators are medicinal products used as a reference in a clinical trial vis-à-vis the substance being tested.

50. 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 “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.

1.14 Question: What are the regulatory requirements for IMPs?

51. **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).

1.15 Question: What is considered to be an auxiliary product?

52. **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[13] 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[14]).

53. 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.

54. 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.

55. 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.[15]).

1.16 Question: Can a study be considered as clinical trial within the scope of Regulation (EU) No 536/2014 if it starts after administration/exposure of the investigational medicinal product has finished?

56. **Answer:** Yes. The start of a clinical trial is defined in Article 2(25) of Regulation (EU) No 536/2014 (see also Q&A 10.1). Normally, it is the first act of recruitment of a potential subject, unless otherwise defined in the Protocol. It cannot be excluded, however, that a protocol will set the start of clinical study after the exposure to the investigational medicinal product has finished (eg. clinical study that starts after the administration of an ATMP to investigate long term efficacy and safety; follow-up for late onset side-effects of oncological treatments; or a clinical study comparing response in patient populations on different prior treatment regimes).

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[13] Article 2(2)(8) of Regulation (EU) No 536/2014

[14] https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017_06_28_recommendation_on_axmps.pdf

[15] Recital 53 of Regulation (EU) No 536/2014

57. If the study fulfils the criteria of a clinical trial, and is not a non-interventional study, Regulation (EU) No 536/2014 applies. When assessing whether the study shall be considered as a clinical trial or not, a reference should be made to the algorithm in Annex I.

58. In these cases, since the administration of the medicinal product is finished by the time the trial starts, certain rules relating to the IMP (e.g. on labelling) would not be applicable.

59. In these trials and in particular, when the medicinal product had not been administered in the context of a clinical trial and therefore in accordance with good clinical practice, additional design considerations ensuring data robustness is especially important.

60. In studies when IMP exposure have started before authorization and trial start, the protocol needs to describe particularities for the sponsor in terms of recording study start.

1.17 Question: Which principles of Good Laboratory Practice (GLP) need to be taken into account in clinical trials?

61. **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.

62. 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.

63. 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.

64. 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.

65. 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

66. 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.

1.18 Question: Which principles of Good Laboratory Practice (GLP) need to be taken into account in relation to Advanced Therapy Medicinal Products (ATMPs)?

67. **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.

68. If a pivotal non-clinical safety study[16] 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.

69. 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.

70. 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.

1.19 Question: What are the languages requirements for documents that constitute part I of the application dossier ?

71. **Answer:** The language of the application dossier or parts thereof shall be determined by the Member States. The CTR asks the Member States to consider using a

[16] 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.

commonly understood language in the medical field for documentation that does not go to the subject.

72. Member States have indicated in annex II which documents from the part I (i.e. CTR annex I, sections B to J) can be accepted in English, and what documents are (obligatory) to be submitted in other languages as well.

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?

73. **Answer**: Yes. Such a mixed application is permitted.

74. 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.

75. 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.

76. 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 Question: In cases of applications limited to Part I (article 11) how should a sponsor proceed to submit an application for Part II?

77. **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 CTR Annex I and shall be limited to sections K to R of this Annex.

78. However, if at this stage the sponsor becomes aware of the need for a substantial modification of Part I, different scenarios are possible. Please refer to Q&A 3.6 for further information.

2.3 Question: 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)?

79. **Answer:** An application for the extension of a clinical trial to another Member State can only be submitted:

- after the decision of all MSC which received an initial whole (art 5) or both part I and II in the case of staggered (art 11) application is notified or made by tacit approval under Art 8.6. and at least one of them authorised the trial. This means that in multi-country trials, the last Member State (for staggered applications this is the last MS that received a part II) notifying its decision (or authorised the trial by tacit approval) determines when a subsequent addition of a Member State can be submitted (the "slowest" MS drives the process).

- if there is no ongoing assessment of a part I and part I/II SM in any of the MSC meaning that all MSCs issued a decision on a previous SM application or authorised it through tacit approval (the "slowest" MS drives the process).

80. An application for the extension of a clinical trial to another Member State can be submitted if there is an ongoing assessment of a part II SM in any of the other MSC.

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

81. **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?

82. **Answer**: No.

83. 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?

84. **Answer**: No.

85. 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.

2.7 Question: How will a request for information (RFI) during the initial assessment of a clinical trial application, the assessment of an application for substantial modification and/or the assessment of application for subsequent addition of a Member State concerned be managed?

86. **Answer**: Regulation 536/2014 foresees strict timelines for the assessment of initial clinical trial applications as well as for the assessment of applications for substantial modifications and the subsequent addition of a Member State concerned. Sponsors shall submit the requested additional information within the period set by the Member State which shall not exceed 12 days from the receipt of the request of the reporting MS (part I, Art 6.8, Art. 14.6 and Art 18.6) or MS concerned (part II, Art7.3, Art. 14.7 and Art 20.6).

87. Where the sponsor does not provide the additional information within the period set, the application shall be deemed to have lapsed. Depending on the content of the application (Part I and/or Part II), the request for additional information shall be submitted by the Reporting Member State for part I of the application and by the concerned Member State for part II of the applications.

88. In order to make a timely response by the sponsor feasible and to avoid unnecessary rejections of trial applications, the Reporting Member State (or MSC in case of part II) will formulate requests for information with clear and concise instructions to the sponsor on how to address the considerations stemming from the assessment. In general, it is expected that due to time limitations, only one request for information will be feasible during the assessment period. Therefore, the RFI should focus only on critical issues that need to be addressed by the sponsor as to allow authorization or authorization with conditions and to avoid rejection of the application. In case of an authorization with conditions, it is expected that the conditions in the decision are linked to matters that were raised during the RFI phase. Recommendations to the sponsor by the MSCs can be included with the conclusion of the assessment.

89. As a response to a RFI, the sponsor shall submit a document that includes the responses to all questions. In addition, in those instances, when the response necessitates changes to the clinical trial documentation (e.g. protocol, iMPD, IB), an updated version of the relevant documents including track changes, as well as a clean version of the same documents are expected to be submitted at the same time.

90. Therefore, in order to shorten the assessment and approval timelines and to avoid unnecessary rejections due to time-constraints, the submission of complete and high-quality applications is of particular importance.

2.8 Question: What should be understood by conditions?

91. **Answer**: Regulation 536/2014 allows that the decision on an initial clinical trial application (Art 8.1), or a substantial amendment (Art. 19.1, 20.5, 23.1) or an

addition of a member state concerned (Art 14.3) could be authorised, authorized subject to conditions or be rejected.

92. An authorisation of a clinical trial subject to conditions is restricted to conditions which by their nature cannot be fulfilled at the time of that authorisation.

93. Setting a condition is only possible in case of an application with a positive benefit/risk balance. This means that if the benefit-risk balance is not positive at the time of the authorisation, the application should be rejected.

94. Conditions should be clear and related to an issue already identified in the request for information (RFI) submitted during the assessment. Usually a single round of RFI is expected with a short time for providing an answer. All critical issues raised in the RFI are expected to be solved in the answer to it, including submission of the corresponding updated documents (e.g. protocol, Investigator`s Brochure or IMPD), when the answer imply changes for them (reference to Q&A on RFI). Therefore, CT applications for authorisation should be complete from the initial submission in order to maximize the chance for approval.

95. When all Member States concerned are in agreement, conditions can be used:

- To request additional data not available at the time of the authorisation, e.g. data needed for later trial parts, but not preventing the start of the trial.

- To indicate aspects that the sponsor need to fulfill after the authorisation, e.g. submission of minutes of the safety data monitoring board meetings.

96. Conditions are always included in the respective conclusion section of the EU Portal/database (CTIS) by the reporting MS (part I) or MS concerned (part II), as well as in the assessment report. If the trial is authorised with condition(s) then they are always recorded in the decision of the MSC.

97. Data and/or document upload in CTIS by the sponsor to fulfill a condition is not a substantial modification per se. Therefore it can be done either (1) directly, (through the process of a non-SM relevant for the supervision of a trial) or (2) as (part of) a SM application. This allows sponsors to submit the requested data/documents as soon as possible or when it is requested by the regulatory bodies.

98. It is important to note, however, that submitted data/document provided by the sponsor to fulfill a condition can trigger a request for a substantial modification as part of a corrective measure (CM) from any of the **MSC**. Alternatively, in those cases, when the condition requests that certain information and/or documents are uploaded as a substantial modification, the procedure for the submission of SMs needs to be followed.

2.9 Question: Will the assessment report on part I and II be made public at the time of decision?

99. **Answer**: The clinical trial Regulation (EU) No 536/2014 aims to increase transparency and availability of information on clinical trials through the EU clinical trial portal and database. Article 81 (4) of the Regulation states that the (information in the) EU database shall be publicly available unless one or more exceptions, when

confidentiality is justified, apply (e.g. in order to protect personal data or commercially confidential information).

100. A specific document was developed to give more insight in the application of the disclosure rules.[17]

101. The assessment report is in principle made public at the time of decision, but the moment of publication can be deferred if the sponsor has requested a deferral at the time of the initial submission. In this case, the deferral of assessment reports by the RMS/MSC is only possible if the sponsor has requested a deferral in its initial application and for the same period of time of sponsor's documents (or shorter, as desired by the RMS/MSC).

102. If the sponsor asks for a deferral and this deferral is agreed by the Member States Concerned and/or Reference Member State, when issuing a decision, they can define the timing for the deferral of the publication of the assessment report for the part of their concern. In particular, RMS will be able to set the deferral of publication of assessment report part I and each MSC, including the RMS, will be equally able to set the deferral for their assessment report part II.

103. In any case, Member States Concerned will gain a view-only access to the conclusion and assessment report part II from the other Member States concerned as soon as they submit their conclusions for part II to the sponsor even before a decision is notified by these Member States.

2.10 Question: How will missing or incomplete documents in an application for the subsequent addition of a Member State (article 14) be addressed ?

104. **Answer:** The Clinical Trials regulation (art. 14(3)) foresees a period of 52 days from the date of submission to the notification of the decision for the subsequent addition of a Member State. There is no validation period foreseen in the Regulation.

105. In case, when documents are missing or incorrect (e.g. because they contain nonsensical information or information in a wrong language making the review impossible), the "Request for additional information" process will be used to request the sponsor to submit the necessary documents and information. This implies that the RMS (in case of missing translations of part I documents (art. 14(6), in line with article 26 of the CTR) or the Member State to be added (for missing part II documents (art 14(8)) asks the sponsor to reply within a very short period of time to be set by the Member State.

106. In these cases, the 52 days can still only be prolonged with maximum 31 days as foreseen in art. 14 (6) and (8).

[17] Access here: https://www.ema.europa.eu/en/documents/other/appendix-disclosure-rules-functional-specifications-eu-portal-eu-database-be-audited_en.pdf

2.11 Question: Can the decision on part I of a clinical trial application be changed at the moment of the addition of a Member State Concerned (article 14) ?

107. **Answer:** No.

108. AnsThe Clinical Trial Regulation is clear in its instruction to avoid re-assessment of the application by all the Member States concerned which were involved in the initial authorisation of the clinical trial at the moment of an article 14 application. Additionaly, article 14 does not foresee a mechanism to revise the conclusion on Part I of the assessment report.

109. Nevertheless, art. 14 (5) foresees that the additional Member State concerned (AMS) communicate considerations on the application to the reporting Member State (RMS) and the other Member State Concerned (MSC). A mechanism to request additional information to the sponsor is foreseen, as well as a coordinated review by all MSC and a consolidation by the RMS. At the end, the RMS shall take due account of the considerations and records how the considerations are dealt with.

110. In exceptional cases, the RMS and MSC could therefore decide on additional actions leading to changes of the Part I as a results of those considerations, either through the decision of the AMS or through corrective measures as described in art. 77.

2.12 Question: Can a subsequent addition of a Member State Concerned (art. 14) be submitted if another addition of a Member State Concerned (art. 14) is ongoing ?

111. **Answer:** Yes. However, it is strongly recommended to combine the addition of Member States Concerned in one single application.

2.13 Question: Can a staggered part II initial application be submitted to a MSC if a subsequent addition of a Member State Concerned (art. 14) is ongoing ?

112. **Answer:** Yes. A staggered part II initial application under Art 11 can be submitted to a MSC when there is an ongoing assessment for the addition of a new MSC under Art 14, if the trial has been authorized in at least one of the MSC, which received the full application

2.14 Question: How will missing or incomplete documents in the part II application that follows a previously submitted part I application (article 11 – partial submission) be addressed ?

113. **Answer**: The CTR foresees that an application can be limited to Part I of the assessment report. In this case:

114. - The application for Part I will follow the process as laid down in art. 5, 6 and 7

115. - The subsequent application for Part II will be assessed in accordance with art. 7 and notification of decision will happen in line with art. 8

116. For the subsequent submission of part II, there is no specific validation step described, nor is there a reference to art. 5. When documents are missing or of low quality (e.g. because they contain nonsensical information making any assessment impossible), this should therefore be solved through the Request for Information mechanism described in art. 7 (3). The Member State Concerned will ask the sponsor for the missing documents, within a very short period of time to be set by the Member State.

117. The total timeline can only be prolonged with maximum 31 days as foreseen in art.7(3).

3. SUBSTANTIAL MODIFICATIONS

3.1 Question: How is "substantial modification" defined?

118. **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".

119. 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.

120. 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. In case of doubt, sponsors are encouraged to contact the relevant competent authorities.

121. For a non-exhaustive list of examples of substantial and non-substantial modifications please see Annex III.

122. 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, unplanned introduction of a new IMP, a change of the main objective, primary end point of the clinical trial in all phases or an unplanned and unjustified addition of a trial arm or placebo group are considered as resulting in a new clinical trial and would therefore require a new trial authorization.

3.2 Question: How are the different changes to ongoing clinical trials classified in the Clinical Trials Regulation?

123. **Answer**: In compliance with the CTR, a change to a trial data-field or document in the Clinical Trials Portal and Database is either:

- a substantial modification (art 2.2.13)
- a change relevant to the supervision of the trial (art 81.9) (see Q3.4)
- a non-substantial modification (changes outside the scope of substantial modifications and changes irrelevant to the supervision of the trial)

124. A substantial modification of trial data or document (incl. protocol, IB or IMPD) is defined in Art 2.2.13. of the Regulation and follows the process of chapter III (for further details see also Q&A 3.2).

125. There is no legal basis in the CTR to submit changes other than through an SM or the Art 81.9 route. Therefore there is no functionality developed in CTIS to support changes to trial data/documents other than via an SM or as an Art 81.9 route with notification.

126. In clinical trials with adaptive design (e.g. complex clinical trials), those changes, which are described and specified in the currently authorised protocol can be implemented except in cases where their authorisation through a SM is required by the assessing Member States.

127. When the route to fulfil a condition is not defined by the relevant MS at the time of setting the condition, it is up to the sponsor to decide on the appropriate route (SM or art 81.9) for document or data submission to fulfil a condition.

128. The CTIS will not be able to differentiate between the different types of content changes in a given document. A good example is the IB: a new version of this document can be uploaded as an SM (e.g. with changes impacting benefit/risk in the trial) or as an art.81(9) (e.g. annual update with no significant changes on participants safety and/or benefit/risk in the trial). It is up to the sponsor to define the correct path, depending on the nature of the changes. The guidance will facilitate that task. If a sponsor would disuse this functionality, corrective measures shall be taken by MSC.

3.3 Question: What are the sponsor's responsibilities regarding changes to a clinical trial, which are not substantial modifications (SM), but are relevant for the supervision of the trial (Art. 81.9)?

129. **Answer**: Information on any changes to a clinical trial, which are not SMs but are, nevertheless, 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. For a non-exhaustive list of non-substantial modifications please consult Annex III of this document.

130. Changes relevant to the supervision of the trial (Art 81.9 change) are a new concept under the CTR, which aims to update certain, specified information in the CTIS without the need for an SM application, when this information is necessary for oversight but does not have a substantial impact on patients safety and rights and/or data robustness. Art 81.9 changes can be submitted only if the change does not trigger additional changes, which are expected to be submitted as an SM application. The combination of different art 81.9 changes can cumulate into a change that needs to be submitted as an SM. Specific examples for Art 81.9 changes (e.g. update of sponsor's or CRO contact details) are described in Annex III of this guidance. Importantly, this route can be used to update information to fulfil a condition, depending on the instructions of the RMS (part I conditions) or the MSC (part II conditions).

3.4 What are the sponsor's responsibilities regarding changes to a clinical trial, which are non substantial modifications (NSM)?

131. **Answer:** A non-substantial modification (NSM, i.e. without substantial impact on the safety or rights of the subjects and/or the reliability and robustness of the data and when the information is not necessary for oversight) should not be notified as such. Correction of typos and other administrative changes with no impact on the content and meaning of the information are always expected to be updated as non-substantial modifications.

132. These changes should be implemented during the next substantial modification. Sponsors can provide non-substantial changes whenever the scope of the non-substantial changes matches with the scope of the application under evaluation, meaning:

    a. Part I non-substantial changes can be included in an application with a Part I or Part I and II scope;

    b. Part II non-substantial changes can be included in an application with Part II or Part I and Part II scope.

    c. Both Part I & II changes can be included in an application with Part I (only non-SM Part I will be applicable), Part II (only non-SM Part II will be applicable) or Part I and Part II scope.

133. NSMs need to be listed and identified as NSMs in the cover letter of the SM application. NSMs as a rule are not expected to be described in detail in the cover letter, but in case of confidential information in the description of these NSMs, a redacted cover letter can be submitted as necessary. In case the SM application is rejected and the documents with NSM are reverted, the NSMs should be resubmitted with the next SM application. In the meantime, NSMs will have to be recorded in the Trial Master File and made available on request for inspection purposes as appropriate.

134. Sponsors are encouraged not to submit non-substantial changes during the RFI phase of any ongoing assessment (initial, substantial modification, addition of a new Member State concerned), unless they are required as part of the RFI response.

3.5 Question: When can a sponsor submit a substantial modification concerning Part I and II?

135. **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 a decision on an initial application or an application for substantial modification or addition of a Member State concern is taken (see Q3.1). This implies that no SM request can be assessed while any assessment is on-going for these cases. Therefore, the SM can be assessed only after the decision on the previously submitted application is issued or authorized by tacit approval. This process ensures compliance with the Regulation, the stability of trial documentation for the entire time of the assessment for all assessors and the validity of ongoing assessments and decisions in all MSC.

136. Sponsors are encouraged to submit high quality, full applications.

When can a Part I or Part I+II substantial modification be submitted?

137. Part I or Part I+II SMs can be submitted to MSCs if all the following apply:

- the decision of all MSC which received the initial whole (art 5) or staggered (art 11) application is notified or made by tacit approval under Art 8.6. and at least one of them authorised the trial. This means that in multi-country trials, the last Member State (for staggered applications this is the last MS that received a part II) notifying its decision (or authorised the trial by tacit approval) determines when a part I or part I+II SM can be submitted (the "slowest" MS drives the process)
- there is no ongoing application for an additional MSC (Article 14). In this case, a part I or part I+II SM application cannot be submitted until there is a decision notified on the Art 14 application (as it might have part I implications).
- there is no other ongoing SM assessment (Part I, I+II or II) in any of the MSCs; meaning that all MSCs issued a decision on a previous SM application or authorised it through tacit approval (the "slowest" MS drives the process).-Part II nonSMs for supervision (Art 81.9) can not be updated in CTIS when there is an ongoing Art 14 assessment as this latter might have part II implications.

When can a Part II SM be submitted?

138. A part II SM can be submitted in a MSC if all the following apply:

- this MSC has fully authorised the trial (regardless of whether it was through a full (art 5), staggered (art 11) or additional MS (art 14) application)
- there is no other ongoing SM assessment (Part I, I+II or II) in this MSC.

139. Part II SM assessments can run in parallel in different MSCs. A part II SM can be submitted if there is an ongoing assessment in a different MSC for an additional MSC (art 14, see also Q&A 2.3).

The same rules apply for non-SM and changes relevant to the supervision of the trial (Art 81.9).

3.6 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)?

The functionalities related to the implementation of Article 11 provisions are under development and expected to be available at the time of the first release after the go-live of CTIS.

In the meantime, the following principles apply:

140. **Answer**: If the sponsor has submitted an application limited only to aspects covered by Part I in one or more MSs (article 11), and the subsequent Part II submission was not submitted and decided upon, the sponsor is not allowed to submit a substantial modification concerning Part I, even in the case a positive decision has been taken in another MSC to which a full application was submitted

141. In contrast to the future process, where the sponsor has not submitted a subsequent Part II application to all the MSC but only to one/some of them that have initially received the application, the sponsor can submit a substantial modification if either the following conditions are met:

- All MSC that had received the Part II application have issued their decision (article 8) on the full application (part I and II) and at least one of these MSC have issued a positive decision i.e. meaning that the clinical trial is authorized or authorized with conditions in at least one the MSC and,
- The sponsor has withdrawn the Part I only application in those MSC where the Part II was not submitted (these MSC can be added later through an art. 14 procedure)

The following will apply after the implementation in the CTIS is finalised:

142. Answer: In case of staggered applications (i.e. applications submitted in some of the 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 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

143. The submission and assessment of a SM concerning Part I should take place in all Member States(unless they have issued a negative decision).

144. 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

3.7.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)?

145. **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 Q4.3).

146. 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.

3.8.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?

147. **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 the same substantial modification to multiple trials when these trials use the same documents. In these cases, maintaining the harmonisation of the non-trial specific sections(s) of the IMPD across trials would be advantageous. A robust procedure to support this would have a positive impact on the capacity of sponsors and regulatory bodies to maintain product level documents and information on a portfolio of trials up-to-date in the most efficient manner, and improve overall consistency of product information in EU and at global level (in case of multi-country trials with third countries).

148. Parallel submission of the same SM to enable changes to these documents across trials of the same sponsor and the same IMP is accepted and encouraged (Annex II. A.1). In this case, CTIS functionalities are developed to allow the sponsor to submit one single substantial modification application covering multiple trials, provided that all the substantial modification changes introduced are applicable for all the trials where the SM has been submitted. (e.g. identical changes for all the data and documents included in the SM application). Different language variations of the same change to the same document are acceptable.

149. **The sponsor will be able to submit the multi-trial substantial modification only for those trials that have already been authorized (or authorized with conditions) in all MSC in the case of an article 5 application or at least one MSC in the case of an article 11 submission, and do not have outstanding parallel assessment or pending notification of a decision in CTIS**.

150. In accordance with Article 25 and Annex II of the CTR, the cover letter (submission of several language versions with identical content is acceptable) in the application dossier for the SM shall contain a list of all clinical trials to which the application for substantial modification relates, with the EU trial numbers and respective substantial modification code numbers (to be attributed by the sponsor) of each of those clinical trials.

151. The assessment of the submitted multi-trial substantial modification will be performed and recorded in the EU database independently for each trial by the relevant Member States Concerned and reporting Member States. This means that it might be possible for the sponsor to receive several identical RFIs for several trials. Each trial will show their own record in the EU Database for validation conclusion, assessment part I and part II conclusions, as applicable, and decision of the substantial modification (Q&A 3.1). 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.

152. It is important to specify that submission of multi-trial SM applications will be limited to changes to the IMPD, IB and QP certifications at the time of CTIS go-live. This is to ensure timely implementation of the CTR. Broader use of this functionality (e.g. to master protocol in complex trials or documentation related to a shared screening platform, restart of the trial following a temporary halt) will be explored after the go live of CTIS.

153. There are specific considerations in case of substantial modifications to the Investigational Medicinal Product Dossier (IMPD). The IMPD shall give information on the quality of any investigational medicinal product, the manufacture and control of the investigational medicinal product, and data from non-clinical studies and from its clinical use.

154. The content of the IMPD is described in annex I of the Clinical Trial Regulation (CTR), and contains:

- Quality data
- Non-clinical pharmacology and toxicology data
- Data from previous clinical trials and human experience
- Overall risk and benefit assessment

155. Most of that information is product/substance –specific, with some variance in its extent and details based on the study phase and design (dosages used, blinding, comparator and placebo strategies varying per trial). Part of that information may also be given in the Investigators Brochure (IB). The section with overall risk and benefit assessment is trial-specific. It is possible to cross-refer to the relevant sections in the protocol in the overall risk and benefit assessment section of the IMPD.

156. In addition, whenever it is possible, it is encouraged to cross-refer to the IB for the reference safety information and the summaries of pre-clinical and clinical parts of the IMPD in accordance with Annex I G51

157. Changes to the IMPD, including changes to the quality section, with an impact on participants safety, benefit/risk to the trial or on data robustness shall be submitted as a Substantial Modification (SM) and assessed according to Chapter III of the CTR.

There are two possibilities available to submit SM to the IMPD in multiple trials:

Option 1: Multi-trial substantial modifications

158. In cases of trials using the same IMP (active substance, content/concentration, formulation, route) it is accepted to submit the same substantial modification to multiple trials when these trials use the same IMP and IMPD in accordance to above detailed process

Option 2: Reference to a mother trial

159. In addition, and according to "Table 1 Content of the simplified IMPD" in Annex I of the CTR, if an IMPD has been approved in a MSC for any CT and has not been modified, it is accepted that the IMPD document itself is not submitted for each and every trial with the same IMP in that MSC. The CTR allows this for the different sections of the IMPD and the CTIS enables users to provide a reference for common IMPD-Q or IMPD-efficacy and IMPD-safety.

160. Instead of submitting a complete IMPD in the "daughter" trials, a reference to the "mother" trial containing the approved IMPD could be acceptable under certain conditions. Most importantly, every MSC in every daughter trial has to be a MSC also in the reference ("mother") trial as well. This condition ensures that each MSC in each trial sharing the same IMPD, has the possibility to assess and issue a decision of substantial modifications to the shared IMPD. If this condition is not met, the addition of the reference to the mother trial will be rejected by MSC in the daughter trial. Importantly, Art 14 addition of a MSC to a daughter trial, when the additional MSC is not a MSC in the reference trial will not be possible.

161. Setting up and maintaining a reference from a daughter trial to a mother trial is a manual operation – CTIS does not foresee automatic checks on the conditions. A reference requires information at two levels in the application dossier of the daughter trial:

    1) A link to the "mother" trial needs to be established in the section *Associated clinical trials.* In the case of a different sponsor, a delegation letter needs to be introduced.

2) In the *IMPD* section (quality and/or safety and efficacy), a justification for no IMPD upload needs to be filled in (being a reference to the approved IMPD in another trial)

162. The referencing is a unilateral and non-permanent process in CTIS – there are no automated checks foreseen at the level of the mother trial. There are no requirements at the level of the "mother" trial. The RMS and the MSC need to verify the correctness of the referencing during the validation based on the information provided with the cover letter (preferably in the form of a clear 'association matrix') and check whether the conditions for the referencing (i.e. the MSC is also a MSC in the mother trial) are met. In the case of multinational trials, all MSC need to be MSC in the mother trial as well.

163. Having a single IMPD shared in a portfolio of trials with the same sponsor and same IMPD also means that if a change through an SM is approved to the IMPD in the reference ("mother") trial, the updated IMPD is valid also in all daughter trials referring to the original one. Important to note is that it is not required to submit a SM application to the daughter trial(s) as long as the conditions for referencing remain met.

164. The same principle applies for updates to information in the EU database, which are not substantial modifications but are relevant for the supervision of the clinical trial and introduced through the art. 81.9 route. It is important to note that in this scenario, only the mother trial needs to have no ongoing activities, where in the multi-trial SM scenario, all trials need to be "open" for the submission of the SM.

165. Additional conditions would be that the sponsor submits a list with the cover letter of the SM application an association matrix, where all trials using the IMPD in the reference ("mother") trial are listed and identified as daughter trials to this 'mother' trial. In case there are several IMPs in the mother trial with each its own IMPD, it needs to be specified which daughter trial is referring to IMP. Vice versa, when a sponsor associates a trial as a daughter trial to one or in case of several IMPs to several mother trials, a clear and comprehensive 'association matrix' needs to be submitted with the cover letter each time. The association and the nature of association between the different trials need to be clear at all time. If the sponsor does not comply/misuse these rules, MSC can trigger corrective actions for requiring the submission of a separate per CT SM with the IMPD submitted to the daughter trials and the removal of the reference.

166. Once a CT is ongoing, defining a new mother CT in order to cross-refer to its last authorised version of the IMPD would require a SM in the daughter CT.

167. In the current (20/01/2021) version of CTIS, the IMPD section cannot be changed through an article 81.9 application type. Although this might be possible in a future version, it needs to be emphasised that changes to a reference can only be done through an SM.

<u>End of the reference trial</u>

168. When the end of the reference trial is foreseen, sponsors of the daughter trials may chose to continue using a shared IMPD for several trials. In these cases, the IMPD shall be migrated from the mother trial to a select daughter trial or to a new clinical trial. In this case, the IMPD shall be submitted to the new mother trial via an SM or

in the case of a new trial with the initial application, and once this is approved, the reference to the IMPD in the daughter trials shall be updated via an SM to the IMPD section in CTIS to contain correct information about the new mother trial.

169. This could be done before or, preferably, after the end of the original mother trial as long as the IMPD remains unchanged. On the other hand, changes to the IMPD via SM will require that the document is approved in a mother trial, which is ongoing. This means that by the time of the first SM to the IMPD, all daughter trials shall have the correct reference recorded in their IMPD section.

170. In order to ensure continuity, good communication between sponsors is essential when the daughter trials and the mother trial is conducted by different sponsors.

3.9. How are MSC that have received a partial submission involved in the assessment of part I substantial modifications ?

171. The CTR introduces a high-level of coordination between the MSC for the authorisation of substantial modifications in a clinical trial with the aim to create an agile, robust and predictable assessment process with increased scrutiny through the joint review and harmonised assessment. The assessment process is coordinated by the RMS. Once a RMS was agreed for a clinical trial, it remains RMS for the life-cycle of the trial.

172. An application for a substantial modification can contain multiple changes concerning Part I, Part II or both and will result in a single decision for that application in each MSC (Clinical Trials Regulation Art. 19.1). According to the decision, the substantial modification can be: authorised, authorised subject to conditions or refused.

173. In the case of staggered applications (in accordance with Article 11), all MSCs, which received part I of the initial application would participate in the harmonised assessment of the part I SMs, independently if they received part II as well or not. Those MSCs who receive a part II application later will notify their decision on the "cumulative" part I dossier (initial documents with approved modifications).

(please refer to Q&A 3.6 on the mechanics of submission on part I substantial modifications for Member States in which a partial submission has been done).

174. MSC and RMS can recommend the removal of certain changes or elements from the application during the RFI phase of the assessment process in order to support authorisation of the SM. RFI focus on critical issues (with potential effect on the conclusion/decision, see Q&A 2.7). When the sponsor follows these recommendations, the cover letter should be updated to reflect these modifications to the original application (Annex II.B.3). It is possible to authorise a SM with conditions linked to individual changes. Conditions need to be linked to matters that have been raised during RFI and listed in the conclusion section of the assessment report (Art 6.3) and in the decision of the MSC (Art 8.3). Conditions are set to identify aspects that can not be fulfilled at the time of authorisation (art 19.1, Q&A 2.8.) Setting a condition is only possible if the overall risk/benefit balance of the trial remains positive with all the implemented changes.

3.10.Question: Is the addition of an additional Member State considered a substantial modification?

175. **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).

3.11.Question: Is the deletion of a Member State considered a substantial modification?

176. **Answer:** The deletion of a Member State concerned is not recognized by the Clinical Trials Regulation and is not considered a substantial modification.

177. 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, several 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)).

178. In all scenarios described above, while the clinical trial is ongoing in other MSCs, 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).

3.12.Question: Is the annual safety report considered a substantial modification?

179. **Answer:** No. The annual safety report (ASR) submitted in the Eudravigilance 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.

180. 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.

3.13.Question: Is a change of the Principal Investigator considered a substantial modification?

181. Answer: Yes

182. 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.

3.14.Question: Can a substantial modification of aspects covered by Parts I and II of the assessment report be partially authorised (e.g. only the Part II) ?

183. Answer: No

184. The CTR foresees only one single decision on a SM relating to aspects covered by Parts I and II.

185. This implies that when a Member State Concerned refuses to authorise such a SM either because it disagrees with the conclusion of the Reporting Member State (Part I), or finds that the aspects covered by Part II of the assessment report are not complied with or has an ethics committee issue a negative opinion and therefore, this leads to a refusal of the whole application (part I and part II).

186. In the specific case where a sponsor would not respond in a timely manner to a Request for Information on part II aspects, the lapsing of the application causes the whole SM application (I & II) to lapse for that Member State. This lapsing does not prevent the authorization of the part I SM in the other MSC.

3.15 Question: can there be different decision of a part I SM in different MSc ?

187. **Answer**: Yes

188. The CTR foresees an assessment of a substantial modification of an aspect covered by Part I. In case of multinational trials, all Member States jointly review the

application. The RMS will assess the SM and will submit a conclusion at the end of this asssement.

189. Nevertheless, each Member State Concerned takes an individual decision and can disagree with a positive conclusion by the RMS. This might lead to the situation that for a given clinical trial, several versions of the part I documents exist. The CTIS reflects these versions and contains both an overview of the document versions authorised at trial level and at Member State level.

190. In case of disagreement from one or several Member States to a positive conclusion of a part I substantial modification, the Sponsor can submit subsequent part I substantial modifications. The basis for these SM will be the authorised versions of the part I document. Sponsors are encouraged to carefully review the considerations and justification of the MSC that disagreed on the previous part I SM in order to have one common version of the part I dossier across the MSC.

3.16 How should the change of the source country of an IMP or AxMP be implemented?

191. **Answer:** There are several different scenarios depending on the different sourcing strategies (locally by investigator site or centrally by the sponsor), the authorization status of the medicinal product or the submission of the IMP/AxMP in the application (e.g. by brand name or by substance code, ATC category). These are described in detail in Annex IV of this document.

4. WITHDRAWALS

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

192. **Answer:** The sponsor has the option to withdraw an application for a clinical trial at any time until the decision is made.

193. 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.

194. 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

195. 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 Sates concerned. The sponsor can also withdraw the entire application (also the previously submitted Part I) if he so chooses, until the decision is made.

196. 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 chapter 10 for more information).

4.2 Question: Can an application be re-submitted?

197. **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?

198. **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.

199. 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.

5. SPONSOR/LEGAL REPRESENTATIVE; INVESTIGATOR

5.1 Question: How is "sponsor" defined?

200. **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."

201. 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.

202. 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 responsibilities are shared in case of co-sponsorship?

203. **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.

204. 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.

205. Each task mentioned above can be attributed to one single sponsor. Co-sponsors cannot have a joint responsibility for any of the tasks mentioned above. This means that the responsibility for compliance with each of the above tasks will lie with one single sponsor and cannot be shared by several sponsors. This does not preclude however, that if desired, the sponsor can delegate certain tasks to third parties (see also Q&A 5.4).

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

207. However, in each trial, the sponsor bearing the overall responsibility to ensure compliance with the obligations in the authorization procedure remains responsible to fulfil this role and therefore this sponsor needs to be have full access to the documentation

208. It is assumed that co-sponsors have agreed through a contractual agreement on the exchange of information necessary to allow the responsible sponsor to take informed decision for compliance on behalf of all sponsors during the authorization procedure.

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?

209. **Answer:** A sponsor is defined in article 2(2)(14) of the Clinical Trials Regulation as "an individual, company, institution or organization which takes responsibility of the initiation, for the management and for setting up the financing of a clinical trial".

210. Every clinical trial has to have a sponsor.

211. 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?

212. **Answer:** The sponsor may delegate his trial-related tasks/functions to an individual, company, institution or organization.[18] The Clinical Trials Regulation does not restrict the scope of such delegation and explicitly states that the delegation may concern even *all* sponsor tasks.

213. 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) 536/201 as well as with those of Directive 2001/83/EC in the case of a marketing authorisation application. This applies in particular to ensuring the safety of the subjects and the reliability and robustness of the data generated in the clinical trial.

214. Any trial-related tasks/functions that are delegated to a third party should be specified in a written contract between the sponsor and the third party and when relevant made clear to the investigator (eg. responsibilities regarding safety reporting).

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[18] 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?

215. Answer: No.

216. 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.

217. 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.

218. 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?

219. Answer: Yes.

220. 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.

221. 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?

222. **Answer:** If the sponsor is not established in the EU a legal representative of the sponsor has to be established in the EU.[19]

223. Only one legal representative can act on behalf of one sponsor in one clinical trial.

224. 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

225. It is also acceptable to use an established company as a legal representative.

226. The applicant for the application to the Member State (competent authority and the Ethics Committee) might be different from the legal representative.

227. 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 has the same responsibilities and liabilities as the sponsor and should act on behalf of the sponsor based on a contractual agreement. It also implies that the Member States may address the legal representative with any request related to the conduct of a clinical trial.

228. In order to enable the legal representative to ensure compliance with the sponsor's obligations under the Clinical Trials Regulation it is recommended that the contract obliges the sponsor to provide the legal representative with all necessary information and the legal representative to immediately notify the sponsor in case (s)he becomes aware of any incompliance with the Regulation.

229. 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

5.8 Question: What should be included in the protocol synopsis described in Annex I, D.24 ?

230. **Answer**: Sponsors should include the following information in the protocol synopsis (understandable to a layperson, maximum two pages) to be submitted with the clinical trial application according to Annex I D24. National language requirements for the preparation of the protocol synopsis are in Annex II.

1. **EU trial number and full trial title**

[19] Article 74(1) of Regulation (EU) No 356/2014.

2. Rationale

Specify background and hypothesis of the trial.

3. Objective

Specify the main and secondary objectives of the trial.

4. Main trial endpoints

Describe the main trial endpoints and when they are assessed, *e.g. the main trial endpoint is the percent change in the number of events from baseline to a specified time or the total number of adverse reactions at a particular time after baseline.*

5. Secondary trial endpoints

Describe the secondary trial endpoints, and when they are assessed *e.g. number of adverse events until 30 days post end of treatment.*

6. Trial design

Describe the design and the expected duration of the trial for the individual subjects, *e.g. double-blind placebo controlled clinical trial where subjects are participating for X weeks.*

7. Trial population

Describe the trial population, indicating the main inclusion criteria including age and disease/healthy volunteer and the main exclusion criteria to protect the subject, *e.g. patients with moderate asthma 18-55 years with normal kidney and liver function and without gastrointestinal ulcer or risk factors for a cardiac arrhythmia; healthy volunteers 18-60 years not exposed to X-Ray examinations during the last 12 months.*

8. Interventions

Describe interventions and treatment duration, also including background treatment if any, *e.g. one group receives a 10 mg tablet of product X twice daily for Z weeks while also receiving product Y as background treatment and the other group receives a placebo tablet twice daily as well as product Y.*

Also describe trial-related diagnostic and monitoring procedures used.

9. Ethical considerations relating to the clinical trial including the expected benefit to the individual subject or group of patients represented by the trial subjects as well as the nature and extent of burden and risks

A benefit-risk analysis should be done for the trial-specific treatments and interventions, clearly explaining if the trial involves an expected individual

benefit (e.g. as required in emergency situations) or a group benefit. When a trial is placebo-controlled, a brief justification should be given. If a non-therapeutic trial is carried out in vulnerable groups, e.g. in minors, incapacitated persons, pregnant or breastfeeding women, their inclusion has to be justified and it should be explained why the risks and burden are considered minimal and why the trial can only be performed in this particular patient group.

The trial-specific risks and burdens for subjects and caregivers (if applicable) related to diagnostic, therapeutic and monitoring procedures should be justified, e.g. the amount and number of blood samples, the number of site visits, physical examinations or other tests, as well as physical and physiological discomfort associated with trial participation.

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?

231. **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?

232. **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 CTR 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[20]).

233. If the trial is prematurely ended/early terminated due to lack of subjects or lack of data to analyze, sponsors have to liaise directly with the relevant National Competent Authorities confirming that no results will be available for a specific trial due to 'lack of subjects' or that the trial was 'prematurely ended' so a statistical analysis cannot be provided (EudraCT & EU-CTR Question and Answer)[21]. In these cases the layperson results summary should exclude primary endpoint data points and include a statement indicating that sound statistical analysis of the information due to insufficient data was not possible.

234. In addition, and according to the abovementioned CT EG guidance document, where a clinical trial has had to close early, the information included in the summary should explain the reason for this, for example, evidence of lack of efficacy, safety events, poor recruitment etc. This is expected to be done in sections 3.2 ("When was this study done?") and as a critical change to the study under 3.3. ("What was the main objective of this study?").

[20] http://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017_01_26_summaries_of_ct_results_for_laypersons.pdf

[21] https://eudract.ema.europa.eu/docs/guidance/EudraCT%20FAQ_for%20publication.pdf

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

235. **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.

236. 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 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?

237. **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.

238. 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.

239. 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

7a DEFINITIONS

7.1 Question: How should the definition of an Adverse event be applied in clinical trials, what should be considered?

240. **Answer:** An adverse event (AE) is defined in Article 2 (32) of Clinical Trials Regulation (EU) 536/2014 as follows: "Any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment." An AE can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (see Section 2A1 of ICH E2A[22]).

241. Any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with any intervention conducted due to the subject participation in the clinical trial, even if not associated to a medicinal product, should also be considered as an AE.

242. Clinically significant abnormal laboratory findings are considered AEs, however abnormal laboratory findings may not be considered as AEs if there is no change compared to baseline values (at randomisation).

7.2 Question: What should be taken into consideration in defining Serious adverse events?

243. **Answer:** A serious adverse event (SAE) is defined in Article 2 of Clinical Trials Regulation (EU) No 536/2014 as follows: "Any untoward medical occurrence or effect that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening or results in death." These characteristics/consequences of a SAE have to be considered at the time of the event. For example, regarding a life-threatening event, this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

244. SAEs include all serious events independent of whether they have a suspected causal relationship to the investigational medicinal product (IMP) or not.

245. "Important medical events" which are medical events that may jeopardise the subject or may require an intervention to prevent a SAE should also be considered as 'serious'.

[22] ICH E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. Link to ICH Efficacy Guidelines: https://ich.org/page/efficacy-guidelines

246. Medical and scientific judgement should be exercised in deciding whether an event is 'serious' in accordance with these criteria.

7.3 Question: What is the difference between an Adverse Event and an Adverse Reaction?

247. **Answer:** An AE may or may not have a causal relationship with the IMP whereas an adverse reaction is any noxious and unintended response to a medicinal product related to any dose of the product. In accordance with ICH-E2A, the definition of an adverse reaction implies a reasonable possibility of a causal relationship between the adverse event and the IMP. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected. It could also be related to the administration procedure when the procedure is an essential part of the IMP administration. For causality assessment, see Question 7.17.

7.4 Question: What is a Serious Adverse Reaction?

248. **Answer:** Serious adverse reactions (SARs) are defined as all noxious and unintended responses to an IMP related to any dose administered that result in death, are life-threatening, require inpatient hospitalisation or prolongation of existing hospitalisation, result in persistent or significant disability or incapacity, or are a congenital anomaly or birth defect (Article 1 of Directive 2001/83/EC). Except for the relatedness (causality), the definitions of SAEs apply (see Question 7.2).

7.5 Question: How should the definition of an Unexpected Serious Adverse Reaction be applied in clinical trials?

249. **Answer:** An unexpected serious adverse reaction is defined in Article 2 (34) of Clinical Trials Regulation (EU) No 536/2014 as a SAR whose nature, severity or outcome is not consistent with the reference safety information (RSI, see Chapter 7 b). A report which adds significant information on the specificity, severity, or frequency of a known and already documented SAR represents as well an unexpected event. See also Question 7.7.

7.6 Question: What is the difference between seriousness and severity?

250. **Answer**: Severity refers to the intensity of the event/reaction and is often classified by its effect on the everyday living of the subject as mild, moderate or severe. Seriousness refers to the outcome or action criteria of an AE or AR and serves as a guide for defining regulatory reporting obligations (see Question 7.4).

251. For example, headache may be severe (prevents everyday activities) but is not considered serious (does not require inpatient hospitalisation, nor results in persistent disability/incapacity/congenital anomaly/birth defect and is neither life-threatening nor results in death).

7 b REFERENCE SAFETY INFORMATION

7.7 Question: What is the purpose of the Reference Safety Information and what should it contain?

252. **Answer**: The Reference Safety Information (RSI) is used for the assessment of the expectedness of all 'suspected' SARs that occur in clinical trials. Therefore, the content of the RSI should be a list of expected SARs and their frequencies. The SARs are classified using Preferred Terms (PTs) according to the Medical Dictionary for Regulatory Activities (MedDRA). These 'expected SARs' should be restricted to 'suspected' SARs that were previously observed more than once, where, after a thorough assessment by the sponsor, reasonable evidence of a causal relationship between the event and the IMP exists. This confirmation should be based, for example, on the comparative incidence with other 'suspected' SARs in all previous and ongoing clinical trials and on a thorough evaluation of causality of the individual reported case. This should be done from the perspective of events previously observed, not on the basis of what might be anticipated from the pharmacological properties of the IMP[23] [24].

253. Suspected SARs that have occurred once are not usually qualified to be included into the RSI, unless there is a very strong plausibility of a causal relationship with the IMP and a robust justification based on medical judgement is provided. A robust rationale is a medical rationale which cannot only be the biological plausibility based on the mechanism of action of the IMP and the presence of risk-mitigation strategies. Importantly, the occurrence of a 'suspected' SAR more than once is not per se an adequate justification for the addition of the term to the RSI as an expected SAR. A thorough assessment by the sponsor is also required for 'suspected' SARs that have occurred more than once, and **justification for the addition to the RSI should be submitted alongside the proposed addition**. Explicit justification should be provided when 'suspected' SARs are included in the RSI with an unknown frequency on the basis of postmarketing experience. It might be acceptable that "suspected" SARs based on the post-marketing experience are added in the RSI only for the same indications or relevant indications (the same therapeutic areas and same expositions). However, if the indications of post-marketing experience are different of the clinical trial, the RSI should be based only on the clinical experience in the relevant

[23] ICH E2A Clinical safety data management: Definitions and standards for expedited reporting, section 2. Link to ICH Efficacy Guidelines: https://ich.org/page/efficacy-guidelines

[24] Annex III (6) Clinical Trials Regulation (EU) No 536/2014

indication. Thus, separate RSIs might be needed within one IB for an IMP for different indications.

254. As a general rule, sponsors should not expect an IMP to cause fatal SARs. Thus, fatal SARs should usually be considered unexpected even if previous fatal SARs have occurred.

255. Fatal SARs can only be considered expected for IMPs with a marketing authorisation (MA) in the EU/EEA/ICH country, when it is clearly stated in the table or list of ARs in section 4.8 of Summary of Product Characteristics (SmPC) that the IMP can cause these fatal SARs. Thus, the RSI of a product that has not received a MA in the EU/EEA/ICH country should never include fatal SARs.

256. **If a SAR is added** to the RSI section of an IB, an update of the benefit/risk statement for clinical trial subjects should be provided and **adequate risk minimization measures should be proposed in the updated clinical trial protocol**(s). This is especially relevant if it is fatal in case where IMP has marketing authorisation (see above).

7.8 Question: Which document should contain the Reference Safety Information?

257. **Answer**: The RSI of an IMP without a MA in the EU should always be a clearly separated specific section within the Investigator's Brochure (CTR Annex III 2.2.7) (IB[25]).

258. The RSI section within the IB should be a clearly-identified section titled "*Reference safety information"* which may either be integrated into section 7 of the IB 'Summary of Data and Guidance for the investigator' (please see ICH E6[26]) or be a new section, e.g. section 8. When the RSI is contained within an IB, the sponsor should clearly indicate that the RSI section outlines expected SARs for regulatory reporting purposes and that the information within the RSI section does not present a comprehensive overview of the safety profile of the IMP(s).

259. For an IMP with a MA in the EU, which is used according to the MA, the RSI should be section 4.8. 'Undesirable Effects' of the appropriate SmPC[27]. If the IMP has MA in several Member States (MSs) concerned with different SmPCs, the sponsor should justify its selection of the most appropriate SmPC as the RSI, with reference to subject safety. An EU SmPC should be submitted, but if it does not fit the trial, a SmPC from other ICH countries may be submitted. The EU SmPC is preferred over product information from other ICH countries. If an SmPC is used as the RSI, the study protocol should be compliant with the risk mitigation measures included in the

[25] Annex I (30) Clinical Trials Regulation (EU) No 536/2014

[26] ICH E6 Good Clinical Practice. Link to ICH Efficacy Guidelines: https://ich.org/page/efficacy-guidelines

[27] Annex I (28) Clinical Trials Regulation (EU) No 536/2014

SmPC. The SmPC should be submitted as a separate document (i.e., Section 4.8 of the SmPC should not be copied into the RSI of the IB; and Sponsors must use either the SmPC section 4.8 or the dedicated part of the IB (RSI) for the assessment of expectedness of SARs. In the latter case, the RSI section must be compliant with the guidance of this document.). Note that whereas section 4.8 of the SmPC aims at giving an exhaustive picture of the safety profile of a medicinal product, the purpose of the RSI is to provide clarity to all stakeholders of which SARs are unexpected and therefore qualify for expedited reporting. Thus, separate RSIs might be needed within one IB for an IMP for different indications.

260. In the case where a sponsor has applied for a marketing authorisation for an IMP for the indication under study and the IMP has been granted a positive opinion by the CHMP but not yet the Commission's decision on its MA or is not yet marketed, the RSI should be a section in the IB.

261. If it is proposed to use an IMP outside the (EU) indication of MA within the trial, section 4.8 of the SmPC for the IMP(s) could be used as the RSI, if scientifically justified by the sponsor in the clinical trial application cover letter. Otherwise the RSI should always be a clearly separated specific section within the IB as detailed above.

262. The Company Core Data Sheet (CCDS) is not accepted as RSI by itself. However, CCDS may be contained in an appendix to the IB and include the RSI as a separate clearly identified section titled, e.g., "Reference safety information for assessment of expectedness of serious adverse reactions". In that case, the RSI section must be compliant with the guidance of this document.

263. The location of the RSI should always be clearly indicated in the cover letter of the CT application.

7.9 Question: Which format should be chosen for the Reference Safety Information?

264. **Answer**: The RSI should be presented in the form of a table, where the nature of the 'expected SARs' must be listed by MedDRA body System Organ Class (SOC) and Preferred Terms (PTs; lower level terms within the PTs will also be considered expected) followed by the frequency. The latest MedDRA version should always be used. The frequency must be calculated on an aggregated level and should be based on the previously observed SAEs considered related to the IMP by the investigator or analysed by the sponsor as SAR or SUSAR (events upgraded by sponsor). The frequency numbers are preferred to be in categories similar to the SmPC, section 4.8[28]. When there is an insufficient number of subjects exposed to the IMP to use these categories or low numbers (e.g., two) of the expected SARs observed, the numbers of each 'expected SAR' should be provided, together with the number of patients exposed (refer to Table 3 below for example).

[28] Eudralex Volume 2C – Regulatory guideline (https://ec.europa.eu/health/documents/eudralex/vol-2_en)

265. Inclusion of events seen in a post-marketing setting is acceptable. However, when such events are included it must be clear that only those previously seen as serious are included. A frequency of "unknown" is not allowed. It is acknowledged that the true frequency category may not be known, therefore, absolute numbers for each event should be provided. Alternatively, it is acceptable to provide a frequency category that has been calculated as per the "Adverse reactions from spontaneous reporting" guidance as used for an SmPC.[29]

Example of an RSI table:

Table 3 Serious Adverse Reactions for the IMP considered <u>expected</u> for safety reporting purposes.

SOC	SARs	Number of subjects exposed (N) = 328		
		All SARs	Occurrence of fatal SARs [1)]	Occurrence of life-threatening SARs [1)]
		n* (%)	n (%)	n (%)
Gastro-intestinal disorders	Intestinal perforation	9 (2.7)	3 (0.9)	6 (1.8)
Hepatobiliary disorders	ALT increase	12 (3.6)	Not applicable	Not applicable
	AST increase	9 (2.7)	Not applicable	Not applicable
Cardiovascular disorders	Myocarditis	33 (10.0)	Not applicable	2 (0.6)
	Bradycardia	(Rare) [2)]	Not applicable	Not applicable

n = number of subjects who have experienced the SAR

1) If in exceptional cases (see Question 7.7) individual fatal and life-threatening SARs are considered expected for an IMP, the respective columns should always be included in the table. For the rest of the SARs (rows) where fatal/life-threatening outcomes are not expected, this can be stated as "not applicable" with a footnote clarifying that information on numbers for unexpected fatal/life-threatening SARs can be found elsewhere in the IB (see Question 7.13). If no fatal/life-threatening SARs are expected at all for the IMP this must be clearly stated in the RSI, reference needs to be made to other IB sections (see Question 7.13) and the respective columns can be omitted.

2) Bradycardia seen in post-marketing setting only, not in clinical trials. Frequency calculated as per SmPC guidance: event not seen in 328 subjects exposed in clinical

[29] A guideline on Summary of Product Characteristics (SmPC), September 2009, Rev2 (https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf)

trials. Post-marketing events were serious and occurred more than once. Rare: occurrence ≥ 1/10 000 but < 1/1000.

266. If the IMP is under development in different medical conditions or for different populations (e.g., adults and **minors**), separate tables of expected SARs by indication or population **shall be provided**, if the expected SARs are different e.g. for oncology conditions, non-oncology diseases and **for paediatric trials**. It shall also be appropriate to include less expected SARs in the RSI for minors in comparison to the RSI that has been used for the investigation in adults describing only the serious ARs expected for the paediatric population on the basis of the **available experience in the paediatric population**. Regarding young children (especially for children <12 years old), the RSI shall only be based on the experience in the paediatric population and the sponsor may not assume a paediatric safety profile similar to that of adults until paediatric development is complete.

7.10 Question: Which terms should be used for expected SARs in the RSI?

267. **Answer**: The use of medical concepts or unspecific terms in the RSI of an IB, e.g. "Rash", "Infections" or "Arrhythmia" is not acceptable. Only MedDRA PTs e.g. exfoliative dermatitis, urticarial rash or hives, herpes zoster, pneumonia, sepsis, atrial fibrillation are allowed.

268. If there are multiple lower level terms (LLTs) within a single PT, they are all expected (for example if the PT 'pyrexia' is included in the RSI table, then the LLT 'fever' is also considered expected). A product that is known to cause immunosuppression may also lead to infections, however, only the PTs of the type of infections that have been observed should be considered expected, i.e. all infections cannot be considered expected. A 'suspected' SAR should be considered unexpected unless the PT is listed as an expected SAR in the RSI. General PT such as respiratory infection should not be listed in the RSI, but a more specific term such as pneumonia should be listed instead. The investigator should make an effort to give the most specific PT.

7.11 Question: When are 'suspected' SARs considered unexpected because of specificity and/or severity, or frequency?

269. **Answer**: A provision of severity grades using Common Terminology Criteria for Adverse Events (CTCAE) grading system in the RSI is not required. However, reports which present significant information on specificity or severity of a known, already documented SAR represent unexpected events[30] (refer to table 4 for examples).

Table 4 Example of SUSARs and reasons for their reporting

[30] ICH E2A Clinical safety data management: Definitions and standards for expedited reporting. Link to ICH Efficacy Guidelines: https://ich.org/page/efficacy-guidelines

Listed SAR in RSI	'Suspected' SAR in individual Case Reports	Unexpected due to specificity or severity
Acute renal failure	Interstitial nephritis	Specificity
Hepatitis	Fulminant hepatitis	Severity
Cerebral vascular accident	Cerebral thromboembolism	Specificity
Exfoliative dermatitis	Stevens-Johnson Syndrome	Severity and Specificity
Transient increase in liver function tests	Increased liver function tests persisting for several months	Severity
Hypertension	Hypertensive crisis	Severity
Herpes Zoster	Multi-dermal herpes zoster	Severity
Sepsis	Septic shock	Severity
Supraventricular Cardiac Arrhythmia	Atrial fibrillation	Specificity

270. In addition, if the frequency of the suspected SAR is higher than stated in the RSI (higher frequency may be observed as a result of sponsor's analyses), the SAR should be considered a SUSAR. This is applicable for all trials and especially after early phase of development when there are sufficient data available for analysis.

271. Reports which provide additional information on the specificity of an expected SAR should also be considered unexpected[31]. See Table 4.

7.12 Question: What is understood by synonymous medical terms and are they allowed in the RSI?

272. Answer: Synonymous medical terms (e.g. somnolence, drowsiness) representing truly the same medical phenomenon. If one of the synonymous medical terms is included in the RSI, it will cover also the other synonymous terms in the RSI. This is not to be confused with different forms of the same medical phenomenon e.g. different forms of rash such as rash generalized, rash maculo-papular, rash papular, rash pustular, etc., which are not considered to be the same medical phenomenon and for which specific PTs in the RSI have to be listed.

273. Table 5 . Examples of synonymous medical terms:

Listed PTs for expected SARs in RSI	'Suspected' SARS in Synonymous medical terms
Pneumonia	Right upper lobe pneumonia
Gastrointestinal bleeding	Melaena

[31] ICH E2A Clinical safety data management: Definitions and standards for expedited reporting. Link to ICH Efficacy Guidelines: https://ich.org/page/efficacy-guidelines

Hypophosphataemia	Blood phosphorus decreased

274.

7.13 Question: What safety information should not be included in the Reference Safety Information, but may be presented elsewhere in the Investigator's Brochure?

275. **Answer**: The following safety information should not to be included in the RSI section of an IB, but should be presented elsewhere in the IB (e.g. in a table, preferably, located in the subsection on Safety under 'Effects in Humans' or in the section 'Summary of Data and Guidance for the Investigator', near the RSI section) if available:

- AEs that were considered unrelated to the IMP by both the investigator and the sponsor,SAEs and non-serious AEs that were considered unrelated to the IMP by both the investigator and the sponsor,
- Non-serious ARs,
- All SARs that are not considered expected (see Question 7.7),
- SARs that have occurred only once, unless there is a very strong plausibility of a causal relationship with the IMP and a robust justification based on medical judgement is provided (see Question 7.7).
- Deaths or SAEs also considered efficacy endpoints in trials with high mortality or morbidity accepted in the authorised protocol by the competent authority to be treated as disease related events and not subject to systematic unblinding. However, careful assessment should be performed in cases where disease related events appear to be enhanced by the IMP. 32
- SARs that are expected for similar products within the therapeutic class, which did not occur in subjects taking the IMP.

276. Information regarding the overall safety profile of the IMP: In accordance with the ICH E6 (R2) guidance, the Summary of Data and Guidance for the Investigator section should provide the investigator with an overview of the potential and identified risks, contraindications, warnings, potential drug-drug interactions, effects on pregnancy and fertility, etc. This section should also discuss measures to mitigate the risks.[33] These risk mitigation strategies should also be reflected in the protocol as appropriate and should be in format of a table presenting serious and non-serious AEs.

[32] Article 41 and Annex III, 2.5 (21) Clinical Trials Regulation (EU) No 536/2014

[33] ICH E6 (R2) Good Clinical Practice. Link to ICH Efficacy Guidelines: https://ich.org/page/efficacy-guidelines)

7.14 Question: What should be included in the section Reference Safety Information in trials if there are no 'expected' serious adverse reactions for the IMP?

277. **Answer**: There may be situations where the IMP is not expected to cause any SARs, e.g. early in the clinical development of an IMP when subject exposure is low. In these cases, a clearly defined section of the IB called RSI should still be present. It should contain a brief text stating that no SARs are considered expected for the IMP by the sponsor for the purpose of expedited reporting and identification of SUSARs in the "Cumulative summary tabulation of serious adverse reactions" in the Annual Safety Report (ASR) for the IMP.

7.15 Question: When is an update of the Reference Safety Information considered approvable (appropriate)?

278. **Answer**: It is highly recommended to update the RSI section of the IB once a year in alignment with the annual reporting period for an ASR (see Chapter 7 d Annual safety report). It is expected that cumulative safety data are reviewed during the preparation of an ASR and used to support the RSI update.

279. It is best practice to submit an updated version of the IB (as a substantial modification application) and a new ASR in parallel, or alternatively to submit the application of substantial modification for the authorisation of the updated RSI within one month after the submission of the new ASR at the latest. The new RSI in the updated IB can only be used for the assessment of expectedness of 'suspected' SARs for the purposes of expedited reporting of SUSARs in a specific trial after the notification of a positive conclusion on the aspects regarding the RSI and after **the first MS concerned** notifies its (positive) decision. Thus, the expectedness of any suspected SAR that occurred before the new RSI is authorised, should be assessed according to the authorised version of the RSI at that time. When the application for a substantial modification of the IB has been given a positive conclusion in a trial, that IB version should be submitted for all other ongoing trials with the IMP, as soon as feasible. For an RSI related to several CTs, see also Answer 287.For the purposes of the identification of SUSARs in the 'Cumulative summary tabulation of serious adverse reactions' in a ASR, Sponsors should use the 'RSI in effect 'at the start' of the annual reporting period (See IB version 6 in Fig. 4). The "RSI in effect at the start of the annual reporting period" should be the version of the RSI in the IB most recently approved in at least one MS where clinical trials are ongoing with the IMP (See IB version 6 in Fig. 4).

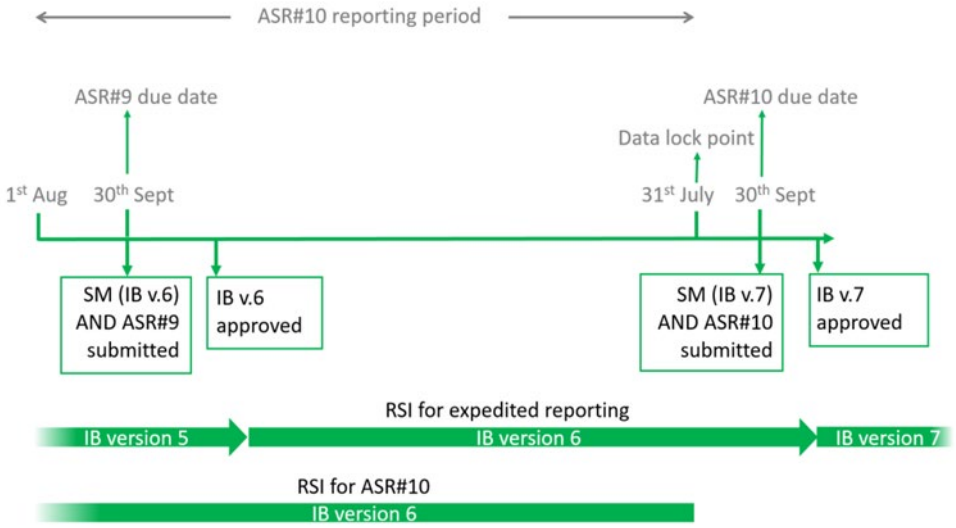

Fig. 4: Example of the IB RSI update following the ASR reporting period.

280. For an ASR (ASR #9 in the example in Fig. 4) with reporting period 1st August – 31st July, the annual review of the IB (version 5 in Fig. 4) should occur following the ASR data lock point (31st July; see Answer 357 for definition of data lock point), in parallel with the preparation of the ASR (ASR due date is 60 days after the data lock point).

281. Where an update to the RSI section is considered necessary by the sponsor, the IB should be updated (version 5 to version 6 in the example) and submitted as a substantial modification (SM) preferably in parallel with (i.e. on the same day or shortly thereafter but no longer than 1 month after) the ASR (ASR#9 in the example). As shown on the picture, the date of submission of the IB version 6 will be different from the date of its approval. It is expected that the period between these two dates will normally not exceed 3 months.

282. Therefore, after the data lock point of ASR#9 and before IB version 6 is approved, the IB version 5 should be used as the RSI for the purposes of the identification of SUSARs in the 'Cumulative summary tabulation of serious adverse reactions' in an ASR. Whereas following approval of IB version 6 by the first MS concerned where a trial with the IMP is ongoing, the new IB version 6 should be used for the purposes of expedited SUSAR reporting and the identification of SUSARs in the 'Cumulative summary tabulation of serious adverse reactions' in ASR#10. In the example above, when the ASR#10 is prepared, IB version 6 should be used as RSI for expectedness assessment (in the reporting period starting with DLP) of all 'suspected' SARs tabulated in the Cumulative Summary Tabulation of Serious Adverse Reactions and both IB version 6 and the new IB (version 7) should be submitted with the ASR[34].

283. Thus, only 'suspected' SARs that are unexpected as per the RSI that was most recently approved should be highlighted as SUSARs in the ASR, and not any 'suspected' SARs that would have been considered to be SUSARs in previous versions of the RSI. It is nevertheless acceptable that some suspected SARs that are

[34] Annex II (2), Clinical Trials Regulation (EU) No 536/2014

considered unexpected in accordance with previous version of the IB will be marked as such during the 'transition' period between two IBs (when the more recent one is not yet approved). Once the new version of the IB is approved, no retrospective reevaluation will be necessary, ie evaluations made at the time of the SUSAR occurrence should not be changed.

284. The RSI used to identify SUSARs in the ASR should be submitted with the ASR, as well as the proposed new RSI, and any changes to the RSI should be detailed in the 'Changes to the Reference Safety Information' section of the ASR (note that if the IB has been updated and there are no proposed changes to the RSI, the new IB should still be submitted)[35].

285. Please be aware that an RSI update (e.g., addition of new expected SAR PTs, change of the frequency of expected SARs, MedDRA updates having an impact on the PTs listed in the RSI, etc.), as well as an update of section 4.8 of a SmPC when it is used as an RSI, is always a substantial modification. However, changes to the format of the table that do not affect the expected SARs or slight modification of exposure rates that do not result in a change in the category of frequency without the addition of new expected SARs and/or new PTs classification are not considered substantial.

286. When submitting a substantial modification that involves an IB or SmPC update, the cover letter must indicate if the RSI is being updated or not. Upon submission of an IB in a substantial modification application containing an update to the RSI, which is not accompanied by a protocol modification, the sponsor should specify in the submission cover letter what risk mitigation measures are already in place in the protocol to manage any new safety issues and if these new safety issues are adequately covered in the subject information leaflet (informed consent form) or if it needs to be updated. References to any parallel ASR submission should also be given in the cover letter. A tracked changes version of the IB should be provided. In cases where justifications for modifications to the RSI are provided in additional documents, these documents should be submitted simultaneously.

287. It is strongly recommended to submit a substantial modification application that includes an updated RSI to all clinical trials which refer to the same RSI at the same time including information in the cover letter about all ongoing CTs to which the SM would apply and for which an application has been or will be submitted.

288. If simultaneous submission is not feasible (e.g., due to another ongoing modification in a trial), in the subsequent SM application, the authorisation status of the SM should be indicated in the cover letter in case any MS has already made a decision on that SM for any of the listed CTs for which such SM would apply. After the first approval, the first approval date by the last MS in the first trial with a positive conclusion and

[35] ICH E2F:Development Safety Update Report. Link to ICH Efficacy Guidelines; https://ich.org/page/efficacy-guidelines

correspondent EUCT number should be stated in a cover letter for subsequent submissions in other ongoing trials or new clinical trial applications.

289. If the RSI is within an IB which is not prepared and updated by the sponsor itself (e.g. for non-commercial sponsors using a company's IB), the non-commercial sponsor should have a written agreement in place with the company in which the updated authorised IB is sent to the other sponsors using the same IMP immediately. The (non-commercial) sponsor should submit the approved IB, together with any of the necessary modifications to the protocol as a substantial modification for their own clinical trial. However, the reporting of new relevant safety issues from the sponsor to other sponsors using the same IMP should not be delayed. .

290. If the RSI is in section 4.8 of the SmPC and a new public version of the SmPC with and an updated section 4.8 becomes available during the trial, it is recommended to submit a substantial modification requesting approval of the update to the RSI immediately. Following approval of the SmPC for use as RSI in at least one MS concerned with ongoing clinical trials, the updated SmPC should be used for the purposes of expedited reporting.

291. An urgent update to the safety data in the IB may be deemed necessary by the sponsor or regulatory authorities at any time during the conduct of a clinical trial. This information can be added to other sections of the IB (preferably to the Safety and Efficacy section under Effects in Humans and/or Summary of Data and Guidance for Investigators section). However, the RSI section of the IB should only be updated following the analyses of SUSARs for ASR (see above Answer 0). It should not be updated multiple times during a reporting period.

7.16 The RSI is not a clearly identified section in the IB accompanying a new clinical trial application. Does the IB have to be amended?

292. **Answer**: Yes, if the RSI is within the IB for an IMP and there is not yet a clearly identified section to this effect, where all expected SARs are included in form of a table (see the answer to question 7.9 for more detail), the clinical trial application risks to be rejected. If there are no 'expected SARs' for the IMP at the point of submission please see question 7.14 for further instructions.

7.17 Question: Who should assess the causality of SAEs between the SAE and IMP and how should it be done?

293. **Answer**: The causal relationship is usually assessed by the investigator. The sponsor can upgrade it (from unrelated to related), but cannot downgrade it. For SUSARs, when the sponsor disagrees with the causal relationship expressed by the investigator

on the IMP, the opinions of the investigator and the sponsor should be recorded in the Individual Case Safety Report (ICSR) in line with ICH E2B[36].

294. In accordance with ICH-E2A[37], the definition of an AR implies at least a reasonable possibility of a causal relationship between a medicinal product and an AE. An AR, in contrast to an AE, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected (see question 7.3). Thus in a clinical trial setting, a causal relationship to the IMP is either considered to be suspected or not for each individual AE which occurs. Numerous methods of causality assessment of ARs have been and are currently used worldwide. Therefore, the ISO ICSR standard allows the possibility to provide several results of causality assessment by using one or more methods of assessment. However, in all cases classifications of an AE except "not related" should be considered that there is a possible causal relationship with the IMP. If an investigator uses the WHO classification of causality, 'unlikely' and 'not' may be considered to be not related. In case of ARs assessed as 'unknown' or 'not assessed' for which the investigator cannot make a decision with regard to relatedness to the IMP the sponsor should consult the reporting investigator and encourage him/her to express an opinion. The causality assessment given by the investigator should not be downgraded by the sponsor. If the sponsor disagrees with the investigator's causality assessment, the opinion of both the investigator and the sponsor should be provided with the report. If (despite all efforts) the causality assessment cannot be made, these SAEs should be considered to be related to the IMP and reported as SUSARs if they are not listed as an expected SAR in the RSI. In general, SAEs with "unknown causality" or "causality not assessed" will not be accepted to support the inclusion of expected SARs in RSI.

7.18 Question: What should be used as RSI for trials with combinations of IMPs?

295. **Answer:** In case of trials investigating a combination of IMPs, the sponsor can either:

- use a single RSI for each IMP included in the combination, that is one RSI per an IMP (the RSIs can be located either in the IB or SmPC as appropriate) or

- create an RSI table for the combination under investigation based on an evaluation of 'suspected' SARs to the same combination of active substances in previous trials

296. The sponsor should explain how the RSI has been compiled and especially in case of new combinations, new indications or new population, take a risk-based approach to including expected SARs in RSI.

[36] ICH E2B Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports (ICSRs). Link to ICH Efficacy Guidelines: https://ich.org/page/efficacy-guidelines

[37] ICH E2A Clinical Safety Data Management:Definitions and Standards for Expedited Reporting. Link to ICH Efficacy Guidelines: https://ich.org/page/efficacy-guidelines

7.19 Question: How should RSI for the development of biosimilar drug products be written?

297. **Answer**: The RSI of the originator may be accepted for a biosimilar product, if it is adequately justified. Please note that, as a general rule, increased frequency of a known SAR has to be reported as SUSAR. In addition, the protocol shall include measures to mitigate both the known risks associated with the originator and the new ones associated with the biosimilar (for example potential risk of reduced efficacy when compared with the originator).

7.20 Question: Which version of the RSI should be used for determining expectedness of 'suspected' SARs for follow up reports?

298. **Answer**: The RSI in effect and approved at the time of occurrence of the 'suspected' SAR should be used to assess expectedness for follow up reports to Eudravigilance (EV) too. SUSARs should not be downgraded in EV on the basis that the RSI was updated after the occurrence of the event.

7c REPORTING OF ADVERSE EVENTS/REACTIONS

7.21 Question: How should relevant information on Suspected Unexpected Serious Adverse Reactions (SUSARs) be reported to Member States?

299. **Answer**: In addition to the data that is required to be reported on SUSARs[38], the sponsor must report all information that is 'relevant', i.e. the information which is necessary in order to:

- verify whether the anticipated therapeutic and public health benefits continue to justify the foreseeable risks, and
- process the report administratively.

300. Medical and scientific judgement should be applied in identifying relevant information. In particular, new administrative information that could impact on the case management is to be considered as 'relevant'.

301. One example of relevant information is any information that may help to detect potential duplicates (e.g. new case identifiers have become known to the sponsor which may have been used in previous transmissions). There is a specific guidance

[38] Annex III, Clinical Trials Regulation (EU) 536/2014

for safety data collection, analysis and reporting in oncology trials[39]. Minor changes of dates or corrections of typographical errors in the previous case version or new versions of MedDRA are non-relevant information as long as they have no impact on the medical content of a case.

302. Note that comparators and placebos are IMPs. Therefore, SUSARs associated with comparators follow the same reporting requirements as for the test IMP. Events associated with placebos will usually not satisfy the criteria for a SUSAR and, therefore, neither for expedited reporting. However, where SUSARs are associated with placebos (e.g., reaction due to an excipient or impurity), the sponsor should report such cases.

303. In case a suspicion of an interaction with the IMP cannot be ruled out for an AE, where Auxiliary Medicinal Products (AxMPs) are also administered, the reporting rules for the IMP apply. See also a specific guidance for AxMPs[40] and Questions 7.5-7.46)

304. When after the initial reporting, it is considered that the event is not a SUSAR, for example due to lack of causality, seriousness, or expectedness (hereinafter this is referred to as 'downgrade'), downgrades by the investigator should be considered as relevant information. However if the sponsor disagrees with the investigator's causality assessment, the sponsor shall not downgrade the investigator assessments. **The opinion of both the investigator and the sponsor should be provided** in the narrative and in the relevant structured ICH E2B data elements of the report[41].

305. Note that safety reporting falls under Clinical Trials Regulation (EU) No 536/2014 or under the provisions on pharmacovigilance (Directive 2001/83/EC or Regulation (EU) No 726/2004) but not under both.

306. An AR to an IMP (or a non-authorised AxMP) occurring in a clinical trial is only to be reported and followed up in accordance with Clinical Trials Regulation (EU) No 536/2014 and in compliance with this document.

307. Rules for SUSAR reporting are established in Clinical Trials Regulation (EU) No 536/2014[42].

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[39] Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/2015/95 Rev.5 https://www.ema.europa.eu/documents/scientific-guideline/guideline-evaluation-anticancer-medicinal-products-man-revision-5_en.pdf)

[40] Safety reporting requirements for AxMPs, (https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017_06_28_recommendation_on_axmps.pdf)

[41] ICH E2B: Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports (ICSRs). Link to ICH Efficacy Guidelines: https://ich.org/page/efficacy-guidelines

[42] Article 42 and Annex III (Safety Reporting) Clinical Trials Regulation (EU) No 536/2014

7.22 Question: Is unblinding necessary in case of SAR being unexpected for either the experimental IMP or comparator IMP? And who should unblind and be unblinded?

308. **Answer**: The sponsor shall unblind the treatment allocation of only the affected subject to whom the SUSAR relates.

309. The sponsor must unblind the treatment for safety evaluation and regulatory reporting purposes if a SAR is unexpected as per the RSI of either IMP, i.e.,either the 'experimental' IMP or the comparator IMP.

310. The unblinding is not necessary for SARs assessed as expected for both, unless needed for the patient safety reasons, (see questions 7.5, 7.10 & 7.11) since the report does not qualify for expedited reporting.

311. The sponsor should have a procedure in place to maintain the blind for persons responsible for the ongoing conduct of the study (such as the management, monitors, investigators) and those responsible for data analysis and interpretation of results at the conclusion of the study. Unblinded information should only be accessible to those who need to be involved in the safety evaluation and regulatory reporting. A separate procedure should exist for SARs unblinded for emergency purposes for the clinical management of SARs by the investigator.

312. As per Clinical Trials Regulation (EU) No 536/2014, Annex III, 2.5. "Unblinding treatment allocation", investigators should only receive blinded information unless unblinded information is judged necessary for safety reasons.

7.23 Question: Which adverse reactions should <u>not</u> be reported as SUSARs?

313. **Answer:** SUSARs should be reported in accordance with Article 42 of Regulation (EU) No 536/2014, the following should not be considered SUSARs:

- SARs related to ***authorised*** AxMPs or concomitant medication received by the subject and without interaction with the IMP (see also Question 7.45-7.46). However, for those SARs, the rules on pharmacovigilance as set out in Directive 2001/83/EC and Regulation (EC) No 726/2004 are applicable. Investigators are encouraged to report such reactions to the drug to the NCAs where the reaction occurred or to the marketing authorisation holder of the suspected medicinal product, but not to both to avoid duplicate submission of individual case safety reports (ICSR),

- Reports of deaths or SAEs also considered efficacy endpoints in trials with high mortality or high morbidity and accepted to be considered as disease related events in the protocol authorised by the NCA; systematic unblinding at the time of the event is not required for those reports[43].

[43] Annex III, section 2, (2.5), (21) in Clinical Trials Regulation (EU) 536/2014

However, careful assessment should be performed in cases where disease-related events appear to be enhanced by the IMP. In accordance with Regulation (EU) No 536/2014, a causality assessment is required for each SAE, and if the investigator considers disease-related event to also be IMP-related and the event is both serious and unexpected then it must be reported as a SUSAR.

- SUSARs occurring in a clinical trial performed (partly or exclusively) in the EU which are not conducted by the sponsor. These SUSARs may come to the attention of the sponsor through individual reports, publications (such as academic literature) or regulatory authorities.

- SARs occurring in a third country outside a clinical trial.

- A SAE which could be associated with the trial procedures and which could modify the conduct of the trial.

- A significant hazard to the subject population such as lack of efficacy of an IMP used for the treatment of a life-threatening disease.

- A major safety finding from a newly completed animal study (such as carcinogenicity).

- Recommendations of the Data Safety Monitoring Board (DSMB), if any, where relevant for the safety of subjects.

- Relevant safety information regarding the procurement or the donor in the case of advanced therapy investigational medicinal products.

314. This information should instead be addressed through the reporting of events other than SUSARs (see Question 7.24). It should be discussed in the IB as well as the ASR or protocol modifications as applicable, e.g. in safety sections of IB other than RSI, especially if relevant to the risk/benefit evaluation. This holds true for their follow-up measures too.

315. The rules on pharmacovigilance as set out in Directive 2001/83/EC and Regulation (EC) No 726/2004 may also apply for this information if the sponsor also owns a marketing authorisation in the EU for a medicinal product containing the same active substance (see guidance in GVP Module VI).

7.24 Question: How to deal with safety issues not falling within the definition of SUSARs?

316. **Answer:** Events may occur during a clinical trial which do not fall within the definition of a SUSAR and, thus, are not subject to the reporting requirements for SUSARs, even though they may be relevant in terms of subject safety. They might require other immediate action, such as:

- Expedite reporting to the sponsor as defined in the protocol

- Regular reporting to the NCAs and Ethics Committees, as required

- Urgent safety measures and their notification[44],
- Notification of unexpected event changing the benefit-risk of the trial[45]
- Substantial modifications of the clinical trial[46] and
- Early termination or temporary halt of the trial and their notifications[47] (See Chapter 10 in this document).

7.25 Question: What should be the terminology, formats and standards for the SUSAR reporting to EVCTM?

7.25.1 Use of terminology

317. For the classification, retrieval, presentation, evaluation and assessment, electronic exchange and communication of SUSAR information to EVCTM, sponsors should apply the following terminology:

(a) the Medical Dictionary for Regulatory Activities (MedDRA) as developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), multidisciplinary topic M1;

(b) the lists of Standard Terms published by the European Pharmacopoeia Commission;

(c) the terminology set out in ISO 11239-standard, 'Health Informatics~~,~~ - Identification of Medicinal Products (IDMP) - Data elements and structures for the unique identification and exchange of regulated information on pharmaceutical dose forms, units of presentation and routes of administration'

318. Sponsors can request the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, the European Pharmacopoeia Commission, the European Committee for Standardisation or the International Organisation for Standardisation to add a new term to the terminology referred to in paragraph 1, where necessary. In such a case, they shall inform the Agency accordingly.

7.25.2. Use of internationally agreed formats and standards

[44] Article 54 in Clinical Trials Regulation (EU) 536/2014

[45] Article 53 in Clinical Trials Regulation (EU) 536/2014

[46] Chapter III in Clinical Trials Regulation (EU) 536/2014

[47] Chapter VI in Clinical Trials Regulation (EU) 536/2014

319. For the description, retrieval, presentation, evaluation and assessment, electronic exchange and communication of SUSARs, sponsors should apply the following formats and standards:

(a) ICH E2B(R2) 'Maintenance of the ICH guideline on clinical safety data management: data elements for transmission of Individual Case Safety Reports until 29 June 2022

(b) ICH M2 standard 'Electronic Transmission of Individual Case Safety Reports Message Specification'.
the current version of the Note for guidance Eudravigilance Human – Processing of safety messages and ICSRs.[49]

320. For the purpose of paragraph 1(a) sponsors the following terminology, format and standard apply as of 30 June 2022:

(a) ISO/HL7 27953-2-standard, 'Health Informatics,-- Individual case safety reports (ICSRs) in pharmacovigilance — Part 2: Human pharmaceutical reporting requirements for ICSR based on the ICH E2B(R3) Individual Case Safety Report (ICSR) Specification and Related Files;

(b) the standard terminology referred to in 7.25.1;

(c) the current version of the EU Individual Case Safety Report (ICSR) Implementation Guide[50.]

321. Sponsors shall report SUSARs electronically to the Eudravigilance database via EVWEB or by electronically using the E2B(R3) electronic ICSR form. In order to help sponsors, for SUSAR reporting, a web-based form had been developed in accordance with Art 40.2 of the CTR in the Clinical Trials Module of the Eudravigilance database ("EVWEB report form"). The form was developed in compliance with Annex II 2.3 of the CTR and on the basis of international guidance documents (including ICH E2B(R3)). The use of this form will support both regulatory compliance with EU law and high level of harmonisation and exchange of safety data. This structured form incorporates the relevant standards and terminology.

322. When, due to lack of resources, direct electronic SUSAR submission to Eudravigilance database is not possible and the sponsor has an agreement with the MSC, it may report to the MSC where the SUSAR occurred (Art 42.3). In this case the NCA shall report SUSARs in EVCTM.

7.26 Question: What is the minimum information to be provided in the SUSAR reports

323. 7.26.1. The minimum information to be provided for an initial report of a SUSAR with life-threatening cases or cases resulting in death, as defined in Annex III in Clinical Trials Regulation (EU) No 536/2014:

- a valid EudraCT/EUCT number
- a sponsor study number

- an identifiable coded subject
- an identifiable reporter
- a SUSAR (reaction as Meddra LLT)
- a suspect IMP (including active substance name code)
- a causality assessment

324. In addition, in order to properly process the report, the following administrative information should be provided (Annex III in Clinical Trials Regulation (EU) No 536/2014):

- the sender's (case) safety report unique identifier
- the receipt date of the initial information from the primary source
- the receipt date of the most recent information
- the worldwide unique case identification number
- the sender identifier

7.26.2. The minimum information that need to be completed in the *full individual case reports* of SUSARs (initial and follow-up reports):

325. There are specific fields in individual case safety reports (ICSRs) that absolutely need to be completed for a valid SUSAR submission, some are yes/no questions. These fields are there to collect the necessary data for appropriate safety reporting as a prerequisite to ensure sufficient trial participants safety. At the same time, for high safety standards in EU/EEA clinical trials, sponsors shall ensure that individual case safety reports of SUSARs are as complete as possible and shall communicate the updates of those reports to EVCTM in an accurate and reliable manner.

326. Sponsors shall record the details necessary for obtaining follow-up information on individual case safety reports. The follow-up of reports shall be adequately documented.

327. When reporting SUSARs, sponsors shall provide all available information on each individual case, including the following:

(a) administrative information: report type, date and a worldwide unique case identification number as well as unique sender identification and sender type; the date on which the report was first received from the source and the date of receipt of the most recent information, using a precise date. When applicable, other case identifiers and their sources, as well as references to additional available documents held by the sender of the individual case safety report;

(b) if the SUSAR has been reported in the medical literature, including a reference would be considered as good practice (if a reference is provided it should be in accordance with the 'Vancouver style' as developed by the International Committee of Medical Journal Editors (1));

(c) trial type (referred to "study type" in the ICSR form), trial name and the sponsor's study number and valid EU trial number (EudraCT/CTIS number);

(d) information on the primary source(s): information identifying the reporter (, including country and professional qualifications);

(e) information identifiable coded participants (referred to "patient" in the ICSR form) (and parent in the case of a parent-child report), including gender and age at the time of the onset of the first reaction.Gestation period at the time of exposure and when reaction/event was observed in the foetus. When relevant, theweight, height , last menstrual date should be completed;

(f) relevant medical history and concurrent conditions;

(g) the name of the investigational medicinal product(s) or non-authorised auxiliary medicinal product (s) suspected to be related to the occurrence of the SUSAR, including interacting medicinal products or, where the name is not known, the active substance(s) and any other characteristics that allow for the identification of the medicinal product(s), including the pharmaceutical form and (parent) route(s) of administration, indication(s) for use in the case, dose administered, start date and end date of administration, actions taken with the medicinal product(s), effect of the dechallenge and rechallenge for suspect medicinal products;

(h) for biological medicinal product(s), the batch number(s);

(i) concomitant medicinal products, identified in accordance with point (g), which are not suspected to be related to the occurrence of the adverse reaction and past-medical drug therapy for the patient (and for the parent), where applicable;

(j) information on the SUSAR(s): start date and end date of the SUSAR(s) or duration, seriousness, causality assessment of the investigator and the sponsor including assessments of life-threatening/fatal nature of the event if relevant, outcome of the SUSAR(s) at the time of last observation, time intervals between suspect investigational medicinal product administration and start of SUSAR, the original investigator's words or short phrases used to describe the SUSAR and Member State or third-country of occurrence of the SUSAR. The elaboration on assessment of causality (relatedness) by the investigator and the sponsor should include evaluation of possible alternative causes for the event and where appropriate, dechallenge and rechallenge information

(k) results of tests and procedures relevant to the investigation of the patient;

(l) date and reported cause of death, including autopsy-determined causes, in the event of death of the patient;

(m) reasons for nullifying or amending an individual case safety report;

(n) a case narrative, presenting the information (points (a) to (m)) in a logical time sequence, in the chronology of the patient's experience including clinical course,

therapeutic measures, outcome and follow-up information obtained, as well as information of unblinding (date and which treatment the individual participant has received; see Question 7.22). A clear statement has to be given on whether the SAE is unexpected or not (ie, included in the RSI or not).

This should further include the assessment of expectedness of each SUSAR by the sponsor including the grounds for expectedness that is if the event is not listed in RSI or if the frequency/severity/seriousness has increased. Any relevant autopsy or post-mortem findings should also be summarised.

7.27 Question: How should SUSARs of combination IMPs be reported?

328. **Answer**: When the treatment of a clinical trial subject includes a combination of IMPs, the investigator should assess for every SAR if any of the IMPs could have caused it on the basis of medical judgement and without discarding causality for one IMP by only the fact that the suspected AR has been previously described for other IMP in the combination treatment.

329. Where the causality indicated by the investigator is suspected for several IMPs, the sponsor should assess the expectedness of the SAR considering the RSIs of all suspected IMPs when separate RSIs for each IMP are used (see Question 7.18). If the AR is not expected for *all* suspected IMPs (according to the separate RSIs), the SAR should be considered unexpected and reported as a SUSAR.

330. Where RSIs of the combination IMP in the IB or SmPC is used (see Question 7.18), if a suspected SAR is not present in the RSI, it should be reported as a SUSAR. SUSAR should be reported related to the combination, unless it is – in rare cases – known to which IMP the SAR is related to.

7.28 Question: What adverse event reporting should be performed in low intervention trials?

331. **Answer:** Safety recording and reporting in low intervention trials can be simplified from what is described in this document, applying a risk proportionate approach. Risk adaptations to safety reporting refer to documenting of AEs in source documents, recording of AEs in the case report forms (and hence reporting to the sponsor) and to the requirements of immediate (not later than within 24 hours of obtaining knowledge of the event) reporting (of SAEs/SUSARs) by the investigator to the sponsor.

332. Any such adaptation should be clearly stated and justified in the protocol. Please refer to Chapter 4.2 in 'Risk proportionate approaches in clinical trials'[48].

[48] 'Risk proportionate approaches in clinical trials' (https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017_04_25_risk_proportionate_approaches_in_ct.pdf)

7.29 Question: Should SUSARs or ASRs be submitted also to Ethics Committees?

333. **Answer:** Article 42 (SUSARs) and article 43 (ASRs) of the CTR describe the submission through the Electronic database for Safety reporting (Eudravigilance for SUSARs). Additional direct submissions from sponsors to ethics committees are not foreseen in Clinical Trials Regulation (EU) 536/2014.

334. Ethics Committees can be involved in the assessment of safety information by the Member States, if that is the national decision of the individual Member State.

7.30 Question: Should sponsors also send SUSARs to investigators of a clinical trial?

335. **Answer:** The sponsor should promptly notify all concerned investigators/institutions of findings that could adversely affect the safety of the subjects and should expedite the reporting of all SUSARs to all concerned investigators/institutions (ICH E6)[49]. The most important thing is to inform investigators of safety profile changes, not of individual SUSAR reports. For example, information derived from SUSAR reports could be provided via investigators' letters including both an updated benefit-risk evaluation and risk mitigation measures.

336. However, SUSAR reports contain unblinded data that usually should not be sent to investigators. The submission of individual safety reports to investigators may be justified if unblinded data is relevant for the management of the SAR.

337. The safety information for investigators should be concise and practical. Whenever possible, the information on SUSARs should be at least a list of SUSARs that occurred at their MS, national territory, together with a summary analysis of safety profile and updated benefit risk for the ongoing clinical trials.

7.31 Question: When do requirements to record and report safety issues start and end for the investigator and the sponsor?

338. AEs, including SAEs, should be recorded by the sponsor and the investigator from the signature of informed consent to the end of the trial unless otherwise provided for in the protocol.

339. SARs or follow-up information for a SAR that the investigator becomes aware of after the end of the trial should be reported to the sponsor[50].

[49] ICH E6 Good Clinical Practice. Link to ICH Efficacy Guidelines: https://ich.org/page/efficacy-guidelines

[50] Article 41 and Annex III of Clinical Trials Regulation (EU) 536/2014

340. The sponsor shall report all SUSARs from the beginning (see Question 10.1) to the end of the trial (Question 10.12) and after the trial[51], within timelines defined in Article 42 and Annex III of Clinical Trials Regulation (EU) No 536/2014.

341. Standard operating procedures should be followed to ensure compliance with the necessary quality standards at every stage of case documentation, data collection, validation, evaluation, archiving, reporting and follow-up.

7.32 Question: How should pregnancies during the trial or medication errors, misuse or abuse of IMPs be reported?

342. **Answer:** All reports of exposure during pregnancy, medication errors, misuse or abuse in relation to the IMP should be recorded by the investigator and notified to the sponsor. General rules of Clinical Trials Regulation (EU) 536/2014 as well as the guidance given in this Question and answer document apply as regards the expedited reporting of SUSARs (including reporting only unexpected SARs), the submission of ASR and the implementation of risk mitigation measures.[52].

7 d ANNUAL SAFETY REPORTS

7.33 Question: What should be the content and format of an Annual Safety Report?

343. Answer: An Annual Safety Report (ASR; Development Safety Update Report, DSUR) should be concise and provide information to assure regulators that sponsors are adequately monitoring and evaluating the evolving safety profile of the investigational drug and appropriately mitigating potential risks relating to the IMP (IMP refers to an active substance in the context of ASRs).

344. The main objective of an ASR is to present a comprehensive, thoughtful annual review and evaluation of pertinent safety information collected during the reporting period related to an active substance under investigation. The ASR, in compliance with 3.18 'Overall Safety Assessment' of the ICH E2F[53], and Chapters 2 and 3 of the guideline, is expected to contain interval line listings of the serious adverse reactions (SARs) and cumulative summary of serious adverse events (SAEs) (see also Question 7.41). In addition, ASRs will also contain a list of deceased and trial participants who dropped out in association with an AE. Periodic case line listings of SARs, as well as region-specific listings based on case reports, contain case (i.e., Worldwide Unique Case Identification Number) and study ID information and allow

[51] Article 42c of Clinical Trials Regulation (EU) 536/2014

[52] Annex III, section 2.1 (2) of Clinical Trials Regulation (EU) 536/2014

[53] ICH E2F Development safety update report. Link to ICH Efficacy Guidelines: https://ich.org/page/efficacy-guidelines

the assessors and inspectors at the national competent authority (NCA) to perform further evaluation of the specific serious cases presented.

345. Without this information NCAs would not be able to assess serious individual cases and enquire further information from the sponsors. In order to comply with Art 43.3 of the CTR and protect patients' rights, SARs in the line listing should be identified by case ID and study ID without including subject ID in this document. Similarly, the case ID and study ID when reporting the list of deceased and trial participants who dropped out in association with an AE should not allow the identification of natural persons.

346. In case authorities would decide to investigate a specific SAR and ask information or data which can be found in the patient's file, the sponsors and/or investigator will be able to assist this investigation without revealing the subject ID and thus rendering the data in the ASRs as anonymous to authorities (in the sense of Recital 26 of the GDPR) in the context of safety reporting under CTR as long as subject ID is not included in line listings and not provided to authorities.

347. An ASR should be provided per IMP or a combination IMP[56] (see also Answer 350.34).

7.34 Question: When and for how long should the sponsor submit the annual safety report?

348. **Answer**: An ASR should be submitted, to the EV database[54], from the start of the first clinical trial in any MS of the EU/EEA until the end (Question 10.12) of the last clinical trial conducted by the sponsor with the IMP in any MS of the EU/EEA. When submitting an ASR, the MSs concerned where any clinical trial is still ongoing should be indicated. If all trials with the IMP are on hold for over 1 year, the sponsor may submit a simplified ASR.

349. Submission of ASR is not required in case the sponsor is conducting only a single short trial less than one year long with the IMP. Sponsors need to submit an ASR also for IMPs investigated in Phase IV, low intervention trials and long-term follow-up trials.

7.35 Question: How should an ASR for combination including multidrug therapies be submitted?

350. **Answer**: As a main rule, separate ASRs may be prepared for each IMP of a combination and data on clinical trial safety can be included in each ASR[55].

[54] Module for ASR submission will be in the Clinical trial information system (CTIS)

[55] ICH E2F Development safety update report. Link to ICH Efficacy Guidelines: https://ich.org/page/efficacy-guidelines)

351. In general, a single ASR should be prepared for clinical trials involving a development of a (fixed) combination product.

352. In exceptional cases (e.g., in academic studies), a single ASR for the trial may also be prepared for multi-drug therapy. Given the potential complexities it is not possible to provide specific guidance that addresses all the different situations. However, some advice can be found in section 2.5 of the ICH E2F[59].

7.36 Question: What is a Development International Birth Date (DIBD), how is it defined, and what is it used for?

353. **Answer:** The development international birth date (DIBD) is used to determine the start of the annual period for the ASR. This date is the date of the sponsor's **first authorisation to conduct** the first clinical trial with the IMP in any country – **worldwide**.

354. The start of the annual period for the ASR is the month and date of the DIBD (e.g., when the DIBD is December 6th, each annual ASR period is from December 6th to December 5th the next year). When the sponsor's first clinical trial is conducted in a country without a formal authorisation process, the sponsor should designate an appropriate date linked to the commencement of the first clinical trial.

355. To aid harmonisation, it is strongly recommended that the DIBD is indicated by the sponsor within the ASR or in the submission form to the EV ASR module in the clinical trial information system (see ICH E2F section 3.1.).

356. As the international birth date (IBD) of an authorised drug defines the submission of the Periodic Safety Update Report (PSUR) /Periodic Benefit- Risk Evaluation Report (PBRER), IBD and DIBD can be aligned (see also Question 7.36). For EU/EEA harmonised IBD, see the EURD list published on the EMA website[56].

357. The **data lock point** (DLP) for an ASR reporting period is the last day of the one-year reporting period. If desired by the sponsor, the data lock point can be designated as the last day of the month (see ICH E2F section 2.2.[57]) before the month of the DIBD. ASRs should be submitted within 60 days after DLPs.

7.37 Question: Can an ASR be aligned with the PSUR/PBRER International Birth Day (IBD)?

358. **Answer**: When clinical development of a drug continues in the EU/EEA following a marketing approval in any country worldwide, both a PSUR/PBRER and an ASR

[56] EURD list: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/periodic-safety-update-reports

[57] ICH E2F Development Safety Update Report, Section 2.2 Development safety update report. Link to ICH Efficacy Guidelines: https://ich.org/page/efficacy-guidelines

should be submitted as specified by national or regional laws or Clinical Trials Regulation.

359. If desired by the sponsor, an ASR can be prepared based on the PSUR/PBRER and IBD (see also Question 7.35) so that the ASR and the PBRER can be synchronised.

7.38 Question: What DIBD should be used for an IMP with marketing authorisation in the EU/EEA when used in an investigator initiated trial (not by the MAH (marketing authorisation holder))?

360. **Answer:** There are 2 options:

1. Use the (harmonised) **IBD** of the authorised IMP, for products authorised in the EU, the European Union reference dates (EURD) list published on EMA website[58].

2. If the IBD is not available from these lists, it is possible to use a **DIBD**, which is the date of the 1st trial authorisation with this IMP by the sponsor. However, none of the ASR periods should be longer than 1 year.

7.39 Question: When a non-commercial sponsor runs several clinical trials with the same IMP or if different non-commercial sponsors run independent clinical trials with the same non-authorised IMP, is one consolidated ASR needed?

361. **Answer:** For IMPs without a MA it is strongly recommended that the developing company should write a single ASR. Non-commercial sponsors should contact the developer of the IMP and the data of the trials conducted by non-commercial sponsors should be added to the ones generated by trials run by the IMP developer. See also ICH E2F section 2.4.2[59].

362. Submission of one single ASR is strongly recommended if the same IMP is used in several CTs. However, the MS concerned can accept (as an exception) a trial-specific ASR if this is justified.

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[58] EURD list: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/periodic-safety-update-reports

[59] ICH E2F Development Safety Update Report, Section 2.4.2. Link to ICH Efficacy Guidelines: https://ich.org/page/efficacy-guidelines

7.40 Question: Is an ASR required for all drugs in the CT, like comparators, placebos or auxiliary medicinal products (AxMP)?

363. **Answer**: As defined in the Clinical Trials Regulation (EU) 536/2014 article 2(5) an IMP means a medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial. According to Article 43 of the Clinical Trials Regulation (EU) 536/2014, an ASR is required for all IMPs other than placebos. For a reference compound (active or placebo), safety information could also be taken up in the ASR of the test IMP.

364. A separate ASR for an AxMP is not required. However, if necessary, relevant safety information on AxMPs similar to reference compound should be addressed in the ASR of the IMP. See also Question 7.47. All SARs of all required drug types (as of above) in the clinical trials should be included in section 7.2 of the ASR.

365. With regard to format and content please refer to ICH E2F section 2.7 and 3.7 (3.7.1 - 3.7.3)[60]. The latter also covers all drug types with regard to the summary tabulations of SAEs.

7.41 Question: What information is required in the 'Cumulative Summary Tabulations of Serious Adverse Events'?

366. **Answer**: In order to improve the usefulness of section 7.3 of the ASR 'Cumulative Summary Tabulations of Serious Adverse Events' and in addition to the requirements as laid out by ICH E2F, this section should also include the absolute numbers of patients that have been treated as per the column headings of the Cumulative Tabulation of SAEs. This information may be included in the text body of the ASR or preferably within the table itself (as illustrated below), modified from table 6 of ICH E2F guideline.

[60] ICH E2F Development Safety Update Report, Sections 2.7 and 3.7. Link to ICH Efficacy Guidelines: https://ich.org/page/efficacy-guidelines

Table 4.

Cumulative Summary Tabulation of Serious Adverse Events (SAEs)

System Organ Class	Total up to 31-Dec-09			
Preferred Term	[Study drug]	Blinded	Active comparator	Placebo
	n=100	n=1	n=98	n=15
Investigations	**18**	**4**	7	**2**
Alanine aminotransferase increased	9	2	4	1
Aspartate aminotransferase increased	9	2	3	1
Nervous System Disorder	**2**	**2**	**4**	7
Syncope	2	2	4	7

367. If feasible/possible the sponsor should also calculate patient-years of treatment. This information may be especially useful in the interpretation of data when there are substantial differences in time of exposure between subjects randomised to the tested product and comparator(s).

368. A single Cumulative Summary Tabulation of SAEs should be presented for all clinical trials covered in the ASR. A sponsor may also include additional Cumulative Summary Tabulations of SAEs presented for separate populations or indications, however, these must be in addition to the single table covering all trials.

7.42 Question: What 'Region-Specific Information' is required in the ASR in the EU/EEA?

369. **Answer**: As of ICH E2F section 16 of the ASR provides for 'Region-Specific Information'. This section should contain information as required in the EU/EEA region and as outlined below:

- Cumulative summary tabulation of SARs
- List of subjects who died during the reporting period
- List of subjects who dropped out of clinical trials in association with an AE during the reporting period
- Safety signal review, see Question 7.42
- In addition, EuCT numbers of relevant trials are recommended to be listed (together with the protocol code) in the annex of the ASR.

7.43 Question: What *additional* 'Region-Specific Information' is required in the ASR in the EU/EEA?

370. In addition to the above (Question 7.41), a high level overview of the safety review process in the ASR reporting period should be provided as a region-specific appendix. Sponsors should describe what their surveillance processes are for reviewing and identifying potential new safety signals and updating existing safety signals, including but not limited to how often data is reviewed and by whom, what type of data source/format is reviewed and what potential action may arise as a result of the surveillance process. The criteria used for determining the addition or deletion of expected terms to the RSI should also be described here.

371. In addition, the outcome of the safety signal review process during the ASR reporting period should be outlined. Potential new safety signals that were identified should be listed including a brief description of the signal, date when the sponsor became aware of the signal, status of the signal at the end of the reporting interval (closed or ongoing), date when the signal was closed, if applicable, source of the signal, a brief summary of the key data, plans for further evaluation and actions taken (i.e. proposed risk mitigation strategies).

372. The outcome of the safety review should be provided in a tabular format. An example of such a table is presented below (see also Appendix C of ICH E2C(R2)[61]). Other table formats are also acceptable.

373. It is acknowledged that signal evaluation for clinical trials may not always be possible or appropriate, in which case a justification for not including this information should be provided instead.

Table 5. A table format for the outcome of the safety review in the ASR.

Signal term	Date detected	Status (ongoing or closed)	Date closed (for closed signals)	Source of signal	Reason for evaluation & summary of key data	Method of signal evaluation	Action(s) taken or planned
Anaemia	04 March 2015	Ongoing	NA	Single serious case	The signal consisted of a single report of….	Individual case analysis; Review of relevant scientific literature. Reassessment of preclinical and clinical development safety data.	Review at the next Safety Review Team meeting

[61] ICH E2C Periodic Benefit-Risk Evaluation Report. Link to ICH Efficacy Guidelines: https://ich.org/page/efficacy-guidelines

7.44 Question: What RSI should be used for the ASR?

374. See Question 7.15 above.

7.45 Question: Which are the responsibilities of the investigator and sponsor with regards to monitoring and safety reporting of advanced therapy investigational medicinal products?

375. **Answer:** Regarding clinical trials with advanced therapies, general rules as well as IMP specific guidance apply which is contained in the detailed guidelines on good clinical practice specific to advanced therapy medicinal products[62].

7e SAFETY ISSUES OF AUXILIARY MEDICINAL PRODUCTS

7.46 Question: What are the general rules for reporting safety of auxiliary medicinal products (AxMPs)?

376. **Answer**: This section applies to safety reporting requirements in relation to AxMP. In case of a suspected interaction with the IMP the reporting rules for the IMP apply.

377. As the Clinical Trials Regulation (EU) No 536/2014 Article 46 states, safety reporting (referring to *all* adverse reactions) with regard to (authorised) AxMPs shall be made in accordance with Chapter 3 of Title IX of Directive 2001/83/EC, irrespective if they are used in accordance with the terms of the marketing authorisations of these products. Although it is not specified, this applies only to authorised AxMPs. ARs shall be reported to EVPM database.

378. Safety of non-authorised AxMPs (that should be used only exceptionally in clinical trials –in line with Article 59 of Clinical Trials Regulation (EU) 536/2014) is reported according to Article 42 and Annex III of Clinical Trials Regulation (EU) No 536/2014, that is, in line with the same requirements as those provided for the IMP. Accordingly, the ARs related to non-authorised AxMPs shall be reported to the EVCTM database.

379. Safety measures should be taken also due to ASRs of AxMPs in the trial (i.e., protocol modified, as needed).

[62] Guidelines on Good Clinical Practice specific to Advanced Therapy Medicinal Products https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/atmp_guidelines_en.pdf

7.47 Question: Are ASRs required for AxMPs?

380. **Answer:** A separate ASR of the AxMPs is not required. However, any information relating to (authorised or non-authorised) AxMPs which are relevant to the IMP may be included in the ASR of the IMP.

381. All SARs to the non-authorised AxMP(s) should be in the line listings of SARs in ASR of the respective IMP(s) of the clinical trials.

7f SAFETY DURING TRANSITION PERIOD OF CLINICAL TRIALS REGULATION (EU) No 536/2014 IMPLEMENTATION

7.48 Question: How to submit ASRs during the transition period from the EU Directive 2001/20 to the Clinical Trials Regulation (EU) 536/2014?

382. Answer: In case one clinical trial is ongoing in alignment with the Clinical Trials Regulation (EU) 536/2014 while others are under the Directive 2001/20/EC, an ASR should be submitted to the database specified in the regulation. Sponsors are allowed to name all MSs concerned for all ongoing CTs in EU/EEA within Directive as well as Clinical Trials Regulation. Sponsors are still obliged as of CT-3 to submit ASRs to Ethics Committees according to national legislations in MSs with ongoing clinical trials within Directive 2001/20/EC and inform investigators of any new safety data or change in benefit-risk evaluation.

7.49 Question: How to report SUSARs during transition time from Directive 2001/20/EC to EU Clinical Trials Regulation (EU) 536/2014?

383. **Answer:** SUSARs need to be reported to the EV database. Double reporting is to be avoided, unless the NCA has had a national requirement for direct reporting of SUSARs. In addition, despite reporting to NCAs via EV, the reporting obligations as of CT-3 still need to be respected, especially reporting to Ethics Committees according to national legislations in MSs for all IMPs/CTs within Directive 2001/20/EC as well as reporting to investigators (CT-3 Article 109).

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.[63] What does this mean for the requirements as regards manufacturing authorisation?

384. **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.

385. 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.

386. 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?

387. **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[64].

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

388. **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

[63] Chapter IX of Regulation 536/2014

[64] Article 61 (5) of Regulation (EU) No 536/2014

group on clinical trials on "*Auxiliary medicinal products in clinical trials*", rev. 2, June 2017[65])

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.

389. **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 that are not authorised in the EU and do not have a marketing authorisation from a third country that is party to ICH, and are not manufactured in the EU, an authorisation referred to in article 61(1) 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 authorisation according to article 61 of the Clinical trial Regulation) is required.

[65]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?

390. Answer: according to **a**rticle 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 (CTR 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?

391. **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).

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

393. 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.

394. 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)?

395. **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)?

396. **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?

397. **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 CTR 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?

398. **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?

399. **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.

400. 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.

401. 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

402. **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).

403. 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.

404. 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.

405. 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.

406. 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?

407. **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.

408. 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?

409. **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?

410. **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?

411. **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).

412. 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?

413. **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?

414. **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". However, when the protocol specifies circumstances that would determine an early termination of the clinical trial, in case such circumstances occur, the sponsor needs to notify also an early termination of the CT according to Articles 37 or 38 of the clinical trials Regulation, clarifying the reasons to the Member States.

415. In the case of early termination of a clinical trial (CT) for reasons not affecting the benefit-risk balance, such as low recruitment, shortage of drug supply, end of development, provided that treatment options for subjects still participating in the clinical trial would not be compromised, or when no subject has been included, 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, within 15 days of the early termination, according to article 37 of the clinical trial Regulation.

416. An earlier end of a CT which is based on faster recruitment than anticipated, should not be considered as "early termination".

417. There may be cases where a CT is ended earlier for reasons of lack of efficacy or for reasons related with lack of/insufficient quality of the IMP. Both cases would impact the benefit-risk balance and are 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).

418. In all cases of prematurely terminated clinical trials, except when no subject was included in the clinical trial, a summary of results with the relevant available information is expected within one year of the early termination of the CT. The summary should include data from post study follow-up, where applicable.

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

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

420. 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).

421. 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.

422. 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.

423. 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?

424. 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".

425. 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.

426. 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.

427. 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.

428. 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.

429. 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

Please kindly note that detailed information about safety reporting during the transitional period is included in Q&A 7.46 and 7.47 in chapter 7 on Safety reporting

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?

430. **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?

431. **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.

432. 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?

433. **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.

434. 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?

435. **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?

436. **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*[66]). The trial will fall under the regulatory framework of the Regulation as of the tacit approval date (60 days from the submission).

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

437. **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).

[66] http://www.hma.eu/ctfg.html

438. 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 that was issued as part of the authorisation of the clinical trial.

439. 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?

440. **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.

441. 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*[67]). 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.

442. 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.

443. 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:

[67] http://www.hma.eu/ctfg.html

- 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).

444. 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 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 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?

445. **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)?

446. **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*[68]). In order to benefit from the advantages of harmonisation a sponsor should

[68] http://www.hma.eu/ctfg.html

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.

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

447. **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?

448. **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?

449. **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?

450. **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.

451. 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).

452. 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).

453. 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).

11.14 Question: What are the requirements to refer to clinical trial data, collected in clinical trials authorised under the Clinical Trial Directive ?

454. **Answer**: In accordance with article 25(6), data from a clinical can only be submitted in an application dossier if that clinical trial has been registered prior to its start in a public register which is a primary or partner registry of, or a data provider to, the WHO ICTRP. For data from clinical trials that started before applicability of the CTR, it is acceptable as well that the results of the clinical trial have been published in an independent peer- reviewed scientific publication.

455. These new provisions in the CTR impact data of trials in CTAs that have been submitted under the rules from the Directive, but were not made public (e.g. phase I non-paediatric trials). Depending on the time of authorisation of the trial, article 25(6) first or second paragraph will apply.

456. For trials submitted under the CTR that refer to clinical data generated under the Clinical Trial Directive, the registration obligation would be met for trials that have been registered in EudraCT even when these data/information are not made public on the CTR (e.g. phase I non-paediatric trials). This would cover the use of data from phase I trials that ended before the end of the transitional period (article 98(1)) conducted solely in adults and UK was the only MS in the trial (before Brexit). A waiver of Art 25(6) for non-phase I trials authorised under the CTD and being transitioned to CTR is not supported.

11.15 Question: After implementation of the CTR, will EU phase 1 trials meet the CTR transparency requirements as only very limited data will be published in the EU database?

457. **Answer**: Art 25(6) is a shall provision and accepts trial data submission as part of a CTA only if the referenced trial was registered publicly (including registration in the

EU Clinical Trial Register) or the results have been published in a peer-reviewed manner. The last possibility is only there for trials that started before the applicability of the CTR. If a referenced trial is not registered in an ICTRP database or the results are not published, the data can not be used to support an application in the EU under the CTR, irrespective of whether it is a phase 1 trial in adults or not.

458. EU phase I trials will be published, in line with the "Appendix, on disclosure rules", to the "Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014".

459. The main characteristics of trial including WHO ICTRP data fields, will be published at the time of decision on the trial application, independent of the phase of the trial. This fulfils the registration requirement in art. 25 (6).

12. MISCELLANEOUS

12.1 Question: Can the reporting Member State be changed?

460. **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.

461. 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.

462. 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?

463. **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).

Annex I: Decision tree to establish a whether a trial is a "clinical trial"

Note: *this Annex and in particular the definition for a low-interventional trial are 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**	[redacted]
A CLINICAL TRIAL OF A MEDICINAL PRODUCT?					
Is a medicinal product administered before or during the start of the clinical trial	Is it a medicinal product (MP)?(i)	Is it not a medicinal product?	What effects of the medicine are you looking for?	Why are you looking for those effects?	
If a medicinal product is administered before the start of the clinical trial, and it falls under current practice, please go to column E. If a medicinal product is administered before the start of the clinical trial and it falls not under current practice, column E is excluded. If a medicinal product is administered after the start of the clinical trial, please go to column A.	If you answer no to <u>all</u> the questions in column A, the activity is not a clinical trial on a MP. If you answer yes to <u>any</u> of the questions below go to column B.	If you answer yes to the question below in column B the activity is not a clinical trial on a MP. If you answer no to this question below go to column C.	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. If you answer yes to <u>any</u> of the questions below go to column D.	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. If you answer yes to <u>any</u> of the questions below go to column E.	

	A.1. Is it a substance (ii) or combination of substances presented as having properties for treating or preventing disease in human beings? 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? A.3.Is it an active substance in a pharmaceutical form?	B.1. Are you <u>only</u> administering any of the following substances? • Human whole blood(iii); • Human blood cells; • Human plasma; • A food product (iv) (including dietary supplements) not presented as a medicine; • A cosmetic product(v) • A medical device	C.1. To discover or verify/compare its clinical effects? C.2. To discover or verify/compare its pharmacological effects, e.g. pharmacodynamics? C.3. To identify or verify/compare its adverse reactions? C.4. To study or verify/compare its pharmacokinetics, e.g., absorption, distribution, metabolism or excretion?	D.1. To ascertain or verify/compare the efficacy(vi) of the medicine? D.2. To ascertain or verify/compare the safety of the medicine?	[redacted]

(i) Cf. Article 1(2) of Directive 2001/83/EC, as amended
(ii) Substance is any matter irrespective of origin e.g. human, animal, vegetable or chemical that is being administered to a human being.
(iii) This does not include derivatives of human whole blood, human blood cells and human plasma that involve a manufacturing process.
(iv) 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.
(v)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.
(vi) 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.
(vii) Assignment of patients to a treatment group by randomisation planned by a clinical trial protocol cannot be considered as current practice

Annex II: Language requirements for part I documents

Member State		Cover letter	Protocol	Protocol synopsis	Investigators brochure	GMP compliance	IMPD	AMPD	Scientific advice and PIP	Labelling	Fields of the application form
AT	**Accepted in English only :**	YES	YES	NO	YES	YES	YES	YES	YES	NO	YES
	If no, required in the following languages:			German						German (1)	
BE	**Accepted in English only :**	YES	YES	NO	YES	YES	YES	YES	YES	NO	YES
	If no, required in the following languages:			Language of the participants i.e. Dutch, French and/or German						all national languages i.e. French, Dutch, German	
BG	**Accepted in English only :**										
	If no, required in the following languages:										
CY	**Accepted in English only :**	YES	YES	NO	YES	YES	YES	YES	YES	NO	YES
	If no, required in the following languages:			Greek						Greek	
CZ	**Accepted in English only :**	YES	YES	NO	YES	YES	YES	YES	YES	NO	YES
	If no, required in the following languages:			English + Czech						Czech only	
DE	**Accepted in English only :**	YES	YES	NO	YES	YES	YES	YES	YES	NO	YES
	If no, required in the following languages:			German						German	
DK	**Accepted in English only :**	YES	YES	YES	YES	YES	YES	YES	YES	NO	YES
	If no, required in the following languages:									Danish	
EE	**Accepted in English only :**	YES	YES	YES	YES	YES	YES	YES	YES	YES/NO (2)	YES
	If no, required in the following languages:									Estonian	
EL	**Accepted in English only :**	NO	NO (3)	NO	YES	YES	YES	YES	YES	NO	NO
	If no, required in the following languages:	Only Greek	Greek translation	Greek translation						Greek	English and Greek
ES	**Accepted in English only :**	YES	YES	NO	YES	YES	YES	YES	YES	NO	NO
	If no, required in the following languages:			Spanish						Spanish	English + Spanish

Member State		Cover letter	Protocol	Protocol synopsis	Investigators brochure	GMP compliance	IMPD	AMPD	Scientific advice and PIP	Labelling	Fields of the application form
FI	**Accepted in English only :**	YES	YES	YES	YES	YES	YES	YES	YES	YES/NO (2)	YES
	If no, required in the following languages:									Finnish (3)	
FR	**Accepted in English only :**	YES	YES	NO	YES	YES	YES	YES	YES	YES/NO (1)	NO
	If no, required in the following languages:			French						French	French (for the text fields to be made public)
HR	**Accepted in English only :**	NO	YES	NO	YES	YES	YES	YES	YES	NO	NO
	If no, required in the following languages:	Croatian		Croatian						Croatian	English+Croatian
HU	**Accepted in English only :**	YES	YES	Yes	YES	YES	YES	YES	YES	NO	YES
	If no, required in the following languages:			Hungarian						Hungarian	
IE	**Accepted in English only :**	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
	If no, required in the following languages:										
IT	**Accepted in English only :**	YES	YES	NO	YES	YES	YES	YES	YES	NO	YES
	If no, required in the following languages:			English + Italian						Italian	
IS	Accepted in English only :										
	If no, required in the following languages:										
LI	Accepted in English only :										
	If no, required in the following languages:										
LT	Accepted in English only :										
	If no, required in the following languages:										
LU	Accepted in English only :										
	If no, required in the following languages:										
LV	Accepted in English only :										
	If no, required in the following languages:										
MT	Accepted in English only :										
	If no, required in the following languages:										
NL	**Accepted in English only :**	YES	YES	NO	YES	YES	YES	YES	YES	NO	NO
	If no, required in the following languages:			English and Dutch						Dutch	Dutch (for the text fields to be made public)
NO	**Accepted in English only :**	YES	YES	YES	YES	YES	YES	YES	YES	NO	YES
	If no, required in the following languages:									Norwegian (1)	
PL	Accepted in English only :										
	If no, required in the following languages:										
PT	**Accepted in English only :**	YES (5)	YES	YES	YES	YES	YES	YES	YES	NO	YES
	If no, required in the following languages:									Portuguese	

Member State		Cover letter	Protocol	Protocol synopsis	Investigators brochure	GMP compliance	IMPD	AMPD	Scientific advice and PIP	Labelling	Fields of the application form
RO	Accepted in English only :										
	If no, required in the following languages:										
SE	**Accepted in English only :**	YES	YES	NO	YES	YES	YES	YES	YES	NO	YES
	If no, required in the following languages:			Swedish						Swedish	
SI	**Accepted in English only :**	NO	YES	NO	YES	YES	YES	YES	YES	NO	NO
	If no, required in the following languages:	Slovene		Slovene						Slovene	English + Slovene
SK	**Accepted in English only :**	No	YES	No	YES	YES	YES	YES	YES	NO	YES
	If no, required in the following languages:	Slovak / English (Can be bilingual)		Slovak and English						Slovak	

(1) - for an IMP that is only administered by the physician and not handed to the patient, English labelling is acceptable

(2) - YES in case IMP administered at trial site by trial personnel.
- NO in case IMP given to patient to take by him/herself

(3) - Additionally Swedish in case swedish-speking patients are to be recruited

(4) - might be allowed for exceptional cases

(5) -preference for a Portuguese version

Annex III. Classification of changes to ongoing clinical trials

	SM	81.9NSM	NSM	Part I/II
Changes to initial documents				
Sponsor	Change of sponsor entity that involves additional changes: e.g. insurance, legal representative, addition of a new sponsor/co-sponsor	Change of the existing sponsor's name, keeping the same legal entity Change of existing sponsor[69] or co-sponsor legal entity if it does not involve additional changes in the trial documentation apart from administrative changes Changes regarding which co-sponsor is responsible for the tasks referred to in article 72(2) of the Clinical Trial Regulation	Minor changes in the contact details e.g. change of mailing address (like PO Box, not physical change) or email address of a site without impact for the supervision of the trial	

[69] Co sponsor is used in this document in the meaning of Art 72 of the CTR

		Change in the sponsor/co-sponsor contact details (address, email and phone number)[70] Change of contact point to the Union[71], scientific and public contact point (name and contact details)[2]		
Sponsor's Legal Representative within the EEA	Change of legal representative	Change of contact details of legal representative provided that there are no other changes that would be substantial[2]	Minor changes in the contact details e.g. change of mailing address (like PO Box, not physical change) or email address of a site without impact for the supervision of the trial	
Persons/third parties to whom the sponsor has delegated tasks (e.g. CRO)		Addition of a new third party Change of contact details of third party/other persons to whom the sponsor delegated sponsor tasks	Minor changes in the contact details e.g. change of mailing address (like PO Box, not physical change) or email address of a site without	

[70] when timely provision of this information is necessary for adequate supervision of the trial

[71] This term is used in CTIS for the entity who is responsible for being a contact point for receiving all questions from subjects, investigators or any Member States concerned regarding the clinical trial and providing answers to them (Art 72.2b).

		Change in the third party (incl. CRO) contact details (address, email and phone number)[2] Change of delegated tasks[2]	impact for the supervision of the trial	
Upload data/document to meet a condition	Always when the provision or update of data/document if in the decision the condition requested as a SM or exceptionally when the route is not defined by RMS/MSCs but the change has a substantial impact on safety and right or data robustness in the opinion of the sponsor and was not authorised previously (i.e. in the case of trials with adaptive design)	Any other cases, as defined by the RMS (part I) or MSC (part II)[72] (can trigger a SM as part of a corrective action)	--	Part I and/or II
Full title (English or common language for the assessments)	Changes that modify the meaning (normally it is expected to be submitted with other SM with changes the study design)		Administrative changes (typos)	Part I

[72] If the route to fulfil a condition is not defined by the MS, it is the sponsor's responsibility to decide the more appropriate route (SM or art 81.9 change) to submit the necessary documents and/or data

Addition/deletion of non-EEA countries into trial		Inclusion or exclusion of Non-EEA 3rd countries into the application dossier with no additional substantial changes to the trial (e.g. no significant impact on the absolute number of participants in the trial or in a MSC)		

Amendments to the trial protocol				
	1. Change of primary or secondary endpoint; 2. 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. Change in the trial design (e.g. removal of a trial arm, addition of a new trial period (e.g. open label extension) not foreseen in the currently authorized protocol);	1. Significant increase in duration of the overall time of the trial, provided that the following conditions are met[74]: 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. 2. In case of low interventional trials, additional diagnostic or medical monitoring procedure which is not requested	1. Minor clarifications to the protocol. 2. The addition/deletion of exploratory and/or tertiary endpoints as recorded in the TMF with no significant effect on the conduct of the trial. 3. A minor increase in the duration (<10%) of the trial 4. A change in the number of trial participants per Member State if the absolute number of participants in the trial is identical or the decrease/increase is insignificant	Part I

[74] Duration of trial is captured in CTIS by populating data fields for the estimated recruitment start and end of trial dates in EEA. In case of increased trial duration, the sponsor is expected to update the 'estimated end of trial date' field

	6. Addition of a new sub-protocolor trial arm[73] 7. Change of inclusion or exclusion criteria if these changes are likely to have a significant impact on the right and safety of trial participants or the scientific value of the clinical trial (e.g. resulting in changes the overall participants population); 8. Reduction in the number of scheduled subject study visits (including replacement of physical visits with "remote" visits); 9. Introduction or change of a diagnostic or medical monitoring procedure which is likely to have a significant impact on the safety, burden on participants, or scientific value of the clinical trial (including increased number or volume of biological samples taken for the purpose of the trial);	by a MSC if it does not pose more than minimal additional risk or burden to the participants[75].		

[73] if not predefined in the latest version of the authorised protocol

[75] https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017_04_25_risk_proportionate_approaches_in_ct.pdf

	10. Addition/Removal/withdrawal of an independent safety/data monitoring board; 11. Change of IMP/AxMP and/or treatment modalities (mode of administration/duration/frequency/dosing) of IMPs, including the criteria to define treatment modality and stopping rules); 12. A change of study design and conduct which is likely to have a significant impact on primary or major secondary statistical analysis or the risk/benefit assessment 13. Any change (increasing/decreasing) in the absolute number of subjects to be included in the trial unless it is specified in the currently authorised protocol. The change may be due to e.g. an adaptation of the sample size calculation or to maintain a previously defined sample size calculation due to more withdrawals/drop outs than expected. 14. Addition/Deletion of an interim/intermediate analysis unless it is pre-specified in the currently authorised protocol.			

GMP related documents				
Change of source country of IMP/AxMP	See annex IV			

Changes to IMPD- Quality (reference to QWP[76] and BWP[77] guidance, if there are additional items, they will be explained here)				
Changes to the IB/IMPD safety and efficacy (non-quality IMPD[78])				
	1. new toxicological or pharmacological data or new interpretation of toxicological or pharmacological data of relevance for the investigator or with an impact on risk/benefit; 2. new clinical data with impact on the risk/benefit ratio 3. change in the overall risk and benefit assessment and analysis	Annual IB update without safety, efficacy or benefit/risk update		Part I
RSI (If the IB is not an SmPC, it shall contain a	If the RSI is located in the IB, an update to the RSI which has an effect on participants' safety and/or safety reporting and expectedness assessment:		1. changes to the format of the table that do not affect the expected SARs	

[76] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-requirements-chemical-pharmaceutical-quality-documentation-concerning-investigational_en.pdf -- chapter 9

[77] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-requirements-quality-documentation-concerning-biological-investigational-medicinal_en-0.pdf -- chapter 6

[78] CTIS refers to this dossier as "IMPD safety and efficacy". It needs to be noted that in addition to safety and efficacy information it includes also for example the risk-benefit assessment and additional non-clinical and clinical data

clearly identifiable RSI section[79])	i. addition of new expected SAR PTs, ii. change of the frequency of expected SARs, iii. MedDRA updates having an impact on participants' safety and/or on safety reporting and expectedness assessment (e.g. new preferred term (PT)s listed in the RSI) If the RSI is contained in the SmPC, any update of section 4.8. of the SmPC with an impact on safety and/or safety reporting and expectedness assessment (e.g. addition of a new term) Change of the location of the RSI information (e.g. change from IB to SmPC) if an impact on safety reporting		2. slight modification of exposure rates that do not result in a change in the category of frequency without the addition of new expected SARs and/or new preferred terms (PTs)	
Part II document changes				

[79] CTR Annex I. E30

Addition of a site	Addition of a new site Change of the site address with possible impact on suitability		Closure of a site Change of site address with no impact on suitability[80]	
Principal investigator (incl. change of an investigator in case that he or she is the only investigator at a trial site, Art 2.2.16)	Change of PI (Art 15) or its contact details if it is at another new trial site, when this change could impact suitability	Change of contact details of principal investigator (email address, phone number) when timely provision of this information is necessary for adequate supervision of the trial		
Insurance policy	New insurance policy Change in the content of the insurance policy, eg. a new entity for the insurance provider, changes in insurance coverage, conditions and/or insured amounts;		Extension of validity of an already approved insurance certificate	
Other part II documents	1. Significant changes in the content of any documents addressed to participants and/or prospective participants (including advertisement material)[81]		1. Technical and administrative changes (including language corrections) 2. Description of any other agreement than	

[80] This change should be introduced as a NSM into CTIS due to technical reasons

[81] including any significant consequential changes originating from other Part I / Part II documentation

	2. Change in access, disclosure, dissemination, alteration of information and personal data processed related to either participants' or trial team member data (e.g. new, non-EU storage place, compromised); 3. Change in collection and future use of biological samples from clinical trial participants (e.g. new location, outside of EU); 4. Change in financial arrangements with participants and/or site/investigator; 4. Change in the compensation paid to subjects and/or investigator/site for participating in the trial; 5. Change in recruitment arrangements including procedures for inclusion of participants.		the ones as classified as substantial modification between the sponsor and the site during the study duration 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	
Other				
Extension	1. Extension of start of recruitment beyond 2 years to avoid expiration of authorization (Art 8.9)			Part I/II

	2. Extension of temporary halt (art 37, i.e. not for reasons of subject safety) beyond 2 years to avoid end of trial[82]			
Implementation of documentary changes related to urgent safety measures	After the immediate implementation of an USM, (i.e. assessment by EC of urgently implemented changes to the ICF)			Part I/II

Explanatory notes to the table:
Horizontal changes to IMPD affecting several trials using the same drug as IMP: proposal is under development by this group
Terminology in this guidance is aligned with that used in CTIS
Correction of typos and other administrative changes with no impact on the content and meaning are always expected to be updated as non-substantial modifications
In clinical trials with adaptive design (e.g. complex clinical trials), those changes, which are described and specified in the currently authorised protocol can be implemented if their authorisation through a SM was not requested as a condition in the decision[83].
Art 81.9 NSM can be submitted only if the change does not trigger additional changes which are expected to be submitted as an SM application. The combination of different art 81.9 changes can cumulate into a change that needs to be submitted as an SM.

[82] See also Q&A 10.5 in Q&A on CTR

[83]https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2019_02_CTFG_Recommendation_paper_on_Complex_Clinical_Trials.pdf

ANNEX IV: CHANGES TO SOURCE COUNTRY

1. Impact of the change of source country on the regulatory requirements of IMPs and AxMPs without a Marketing Authorisation in EU/EEA (unauthorised IMP/AxMP)

Regulatory requirements with regards to labelling:

- **Article 66:** Labelling required: on the outer and immediate packaging: identification of the CT, the contact person, the medicinal product, information related to the use of the medicinal product in accordance with Annex VI A and B to ensure subject safety and reliability and robustness of the data generated in the clinical trial.

Regulatory requirements with regards to GMP

- **Article 61:** The manufacturing and import of investigational medicinal products in the Union shall be subject to the holding of an authorisation.An I. F: a copy of the manufacturing and import authorisatoin as referred to in Article 61 and a certification by the qualified person in the Union that the manufacturing complies with GMP at least equivalent to the GMP in the Union.[84]

Source country change within EU/EEA, or from Non-EEA to EEA, or from EU/EEA to non-EU/EEA (implies change of manufacturer, manufacturing site and/or manufacturing process)

The change of the source country is a change to be submitted for authorisation as a Substantial Modification[85].

AxMP: The SM submission must cover the change in the **Cover Letter**, **Protocol**, **IB**, SmPC[86] / (simplified) IMPD, GMP/Labelling section and **product section** (whichever is relevant)

IMP: The SM submission must cover the change in the **Cover Letter**, **Protocol**, **IB**, SmPC[87] / (simplified) IMPD, **GMP/Labelling section** and **product section** (whichever is relevant)**.**

[84] unless there are specific arrangements provided for in mutual recognition agreements between the Union and third countries

[85] In exceptional cases, when an application with two manufacturing sites from the same company in different countries is authorised in a clinical trial with the same or equivalent manufacturing process, but identical specifications and with GMP-related documents provided for both sites in the latest approved version of the trial documentation, the change of the source country is no change.

[86] Document equivalent to the European SmPC

2. Impact of the change of source country on the regulatory requirements of IMPs and AxMPs with a Marketing Authorisation in EU/EEA (authorised IMP/AxMP)

Regulatory requirements with regards to labelling:

- AxMP with a Marketing Authorisation in EU/EEA

- **Article 67** : No labelling required additionally to what is described in Article 66(1) or in 2001/83/EC

- **Annex VI** : no labelling requirements described for authorised AxMPs

Optionally and at the sponsor's discretion relabelling might be appropriate e.g. for ensuring the authorised AxMP is dedicated to a specific clinical trial

- IMP with a Marketing Authorisation in EU/EEA

- **Article 67:** Labelling required additionally to what is described in Art 66(1) or 2001/83/EC: identification of the CT and of the contact person on outer and immediate packaging, where the specific circumstances, provided for in the protocol so require to ensure the safety of the subject or the reliability and robustness of data generated in the CT

- **Annex VI , chapter C** (Additional labelling for authorised IMPs)

7. In accordance with Article 67(2), the following particulars shall appear on the immediate and the outer packaging: in accordance with Art. 67 (2) CTR ***(a) name of the main contact; (b) CT reference code allowing identification of the CT site, investigator, sponsor and subject****; (c) 'For clinical trial use only' or similar wording*.

8. The particulars listed in sections A, B and ***C****, …,* ***may be omitted from the label of a product*** *and made available by other means, for example by use of a centralised electronic randomisation system, use of a centralised information system, provided that the safety of the subject and the reliability and robustness of data are not compromised. This shall be justified in the protocol*

1) Sourcing by each Investigator/clinical trial site from EU/EEA market – 'local sourcing'

Sourcing case 1a): Authorised IMP/AxMP identified by active substance (AS) name or ATC code (level 3 to 5)

Definition in application dossier: active substance name or ATC code (including if limited to certain pharmaceutical form(s) and strength(s), where applicable per protocol)

- **Annex I B 7. (h):** in the Cover Letter it will be stated that each investigator/clinical trial site will individually source Authorised AxMP/IMP indicated by the active substance name or ATC code and including if limited to certain pharmaceutical form(s) and strength(s)

- **Annex I D 17. (b):** In the Protocol the active substance name (INN name) or ATC code of the Authorised AxMP/IMP will be stated (according to Annex I D 18), including if limited to certain pharmaceutical form(s) and strength(s).

Supporting rationale: Annex I D 18.: *If a clinical trial is conducted with an active substance available in the Union under different trade names in a number of authorised medicinal products, the protocol may define the treatment in terms of the active substance or Anatomical Therapeutic Chemical (ATC) code (level 3-5) only and not specify the trade name of each product.*

Source country change of Authorised AxMPs/Authorised IMPs within EU/EEA

It is understood that the above way of submission allows for the sourcing of Authorised AxMPs/Authorised IMPs from different MAHs and/or different states of the EU/EEA, provided any language related re-labelling is covered by exemption of art. 61 5. (a) CTR, and provided that there is no change to the pharmaceutical form(s) or strength(s) as covered by the currently authorised protocol version.

The change of the source country is not considered to be a change and as such not to be submitted as NSM, Art. 81.9 NSM or SM.

A change to pharmaceutical form(s) or strength(s) not covered by the currently authorised protocol version is a change to be submitted for authorisation as SM.

Sourcing case 1b): Authorised AxMP/Authorised IMP identified by potential trade name(s)

Definition in application dossier: Trade name(s)

- **Annex I B 7. (h)**: In the Cover Letter it will be stated that each investigator/clinical trial site will source Authorised AxMP/IMP as indicated by trade name(s)

- **Annex I D 17. (b):** In the Protocol the trade name(s) of Authorised AxMPs/Authorised IMPs will be stated.

Source country change of Authorised AxMP/IMP within EU/EEA without change of trade name(s) as currently authorised

The change of the source country is not considered to be a change and as such not to be submitted as NSM, Art. 81.9 NSM or SM.

Supporting rationale:
Annex VI (C 7.) and any language related re-labelling is covered by exemption of art. 61 5. (a) CTR. A risk for the patient safety or reliability/robustness of the clinical trial by such a change is not seen

Source country change of Authorised AxMP/IMP within EU/EEA with change to a trade name not currently authorised.

The change of the source country is a change to be submitted for authorisation as SM.

Authorised AxMP: The SM submission must cover the change in the Cover Letter, Protocol, SmPC, and update the product section as required;

Authorised IMP: The SM submission must cover the change in the Cover Letter, Protocol, SmPC, GMP/Labelling section and update the product section as required.

The change between sourcing with identification by active substance name or ATC code (Case 1a)) and by potential trade names (Case 1b)) or vice-versa is a **change to be submitted as SM**.

2) Sourcing by/on behalf of Sponsor from EU/EEA market – 'central sourcing'

Sourcing case 2a): Authorised AxMP/Authorised IMP identified by active substance name or ATC code (level 3 to 5)

Definition in application dossier: active substance name or ATC code only (including if limited to certain pharmaceutical form(s) and strength(s), where applicable per protocol)

- **Annex I B 7. (h):** In the Cover Letter the active substance name or ATC code will be listed, including if limited to certain pharmaceutical form(s) and strength(s), where applicable per protocol

- **Annex I D 17. (b):** In the Protocol the active substance name or ATC code will be listed, including if limited to certain pharmaceutical form(s) and strength(s)

Supporting rationale: Annex I D 18.: *If a clinical trial is conducted with an active substance available in the Union under different trade names in a number of authorised medicinal products, the protocol may define the treatment in terms of the active substance or Anatomical Therapeutic Chemical (ATC) code (level 3-5) only and not specify the trade name of each product.*

Source country change of Authorised AxMPs/Authorised IMPs within EU/EEA

It is understood that the above way of submission allows for the sourcing of Authorised AxMPs/Authorised IMPs from different MAHs and/or different states of the EEA; provided any language related re-labelling[2] is covered by the currently authorised site for re-packaging/re-labelling of sourced Authorised AxMPs/IMPs if this site will also do any re-labelling after change of source country.

The change of the source country is not considered to be a change and as such not to be submitted as NSM, Art. 81.9 NSM or SM,

A change to pharmaceutical form(s) or strength(s) not covered by the currently authorised protocol version is a change to be submitted for authorisation as SM.

Sourcing case 2b): Authorised AxMP/Authorised IMP identified by potential trade name(s)

Definition in application dossier: Trade name(s)

- **Annex I B 7. (h)**: In the Cover Letter the Authorised AxMPs/Authorised IMPs will be listed with its trade name(s).

- **Annex I D 17. (b):** In the Protocol the Authorised AxMPs/Authorised IMPs will be listed with its trade name(s).

Source country change of Authorised AxMPs /IMPs within EU/EEA without change of trade name(s) as submitted

The change of the source country is not considered to be a change and as such not to be reported as NSM, art. 81.9 NSM or SM.

Rationale:
- The currently authorised site for re-packaging/re-labelling of sourced Authorised AxMPs/IMPs isn't changed
- A risk for the patient safety or reliability/robustness of the clinical trial by such a change is not seen

Source country change of Authorised AxMPs/IMPs within EU/EEA with a change to a trade name not initially submitted

The change of the source country is a change to be submitted as SM.

Authorised AxMP: The SM submission must cover the change in the Cover Letter, Protocol, SmPC, and product section;

Authorised IMP: The SM submission must cover the change in the Cover Letter, Protocol, SmPC, GMP/Labelling section and product section.

The change between sourcing with identification by active substance name or ATC code (Case 1a)) and by potential trade names (Case 1b)) or vice-versa is a change to be submitted for authorisation as SM. Likewise, the change between sourcing by Investigator/Clinical trial site and sourcing by/on behalf of Sponsor or vice-versa is a change to be submitted for authorisation as SM.

Annex V: ABBREVIATIONS (Valid for Chapter 7 on Safety reporting)

AE	Adverse event
AR	Adverse reaction
ASR	Annual safety report
CCDS	Company core data sheet
CTCAE	Common terminology criteria for adverse events
DIBD	Development international birth date
DLP	Data lock point
DSMB	Data safety management board
DSUR	Developmental safety update report
EudraCT	European Union drug regulating authorities clinical trials
EV	Eudravigilance
EVCTM	EudraVigilance clinical trials module
IB	Investigator's brochure
IBD	International birth date
ICSR	Individual case safety report
IMP	Investigational medicinal product
LLT	Lowest level term
MA	Marketing authorisation
MedRA	Medical dictionary for regulatory activities
MS	Member state
NCA	National competent authority
PBRER	Periodic benefit-risk evaluation report
PSUR	Periodic safety update report
PT	Preferred term
PV	Pharmaco-vigilance
RSI	Reference safety information

SAE	Serious adverse event
SAR	Serious adverse reaction
SmPC	Summary of product characteristics
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse reaction