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MEETING DOCUMENT

From: General Secretariat of the Council
To: Working Party on Pharmaceuticals and Medical Devices (Attachés)

Subject: Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on establishing a framework of measures for strengthening Union's biotechnology and biomanufacturing sectors particularly in the area of health and amending Regulations (EC) No 178/2002, (EC) No 1394/2007, (EU) No 536/2014, (EU) 2019/6, (EU) 2024/795 and (EU) 2024/1938 (European Biotech Act)
- Consolidated version of proposed amendments to the Biotech Act (Regulation) on clinical trials on medicinal products for human use (CTR) (Articles)

Delegations will find, in Annex, a consolidated version of the proposed amendments to the Biotech Act (Regulation) on clinical trials on medicinal products for human use (CTR) (Articles) prepared by the Commission.

This working document has been prepared to show the changes in Regulation (EU) 536/2014 on clinical trials on medicinal products for human use ('CTR') as proposed in the Commission proposal COM(2025)1022 final of 16 December 2025. This document has no legal effect.

This working document is based on the consolidated text of the CTR of 10 January 2025.

Deletions are shown in ~~strikethrough~~; replacements and additions are shown in **bold and underlined**.

**REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT
AND OF THE COUNCIL**

of 16 April 2014

**on clinical trials on medicinal products for human use, and repealing Directive
2001/20/EC**

CHAPTER I

GENERAL PROVISIONS

Article 1

Scope

This Regulation applies to all clinical trials conducted in the Union.
It does not apply to non-interventional studies.

Article 2

Definitions

1. For the purposes of this Regulation, the definitions of 'medicinal product', 'radiopharmaceutical', 'adverse reaction', 'serious adverse reaction', 'immediate packaging' and 'outer packaging' set out in points (2), (6), (11), (12), (23) and (24), respectively, of Article 1 of Directive 2001/83/EC apply.
2. For the purposes of this Regulation, the following definitions also apply:

(1) '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

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- 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;

(2) '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.

~~(3) 'Low-intervention clinical trial' means 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~~
- ~~e. 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;—~~

(3) 'Low-intervention clinical trial' means 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, the use of the investigational medicinal product is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products 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.

(3a) ‘Minimal-intervention clinical trial’ means a clinical trial which fulfils all of the following conditions:

(a) the investigational medicinal products are authorised;

(b) according to the protocol of the clinical trial, the investigational medicinal products are used in accordance with the terms of marketing authorisation; 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.

- (4) ‘Non-interventional study’ means a clinical study other than a clinical trial;
- (5) ‘Investigational medicinal product’ means a medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial;
- (6) ‘Normal clinical practice’ means the treatment regime typically followed to treat, prevent, or diagnose a disease or a disorder;
- (7) ‘Advanced therapy investigational medicinal product’ means an investigational medicinal product which is an advanced therapy medicinal product as defined in point (a) of Article 2(1) of Regulation (EC) No 1394/2007 of the European Parliament and of the Council ⁽¹⁾;
- (8) ‘Auxiliary medicinal product’ means a medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product;
- (9) ‘Authorised investigational medicinal product’ means a medicinal product authorised in accordance with Regulation (EC) No 726/2004 or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product, which is used as an investigational medicinal product;
- (10) ‘Authorised auxiliary medicinal product’ means a medicinal product authorised in accordance with Regulation (EC) No 726/2004, or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product, which is used as an auxiliary medicinal product;

(11) ‘Ethics committee’ means an independent body established in a Member State in accordance with the law of that Member State and empowered to give opinions for the purposes of this Regulation, taking into account the views of laypersons, in particular patients or patients’ organisations;

~~(12) ‘Member State concerned’ means the Member State where an application for authorisation of a clinical trial or of a substantial modification has been submitted under Chapters II or III of this Regulation respectively;~~

(12) ‘Member State concerned’ means the Member State where an application for authorisation of a clinical trial or a combined study of a substantial modification has been submitted under Chapters II, IIa or III of this Regulation respectively;

~~(13) ‘Substantial modification’ means 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;~~

(13) ‘Substantial modification’ means any change to any aspect of the clinical trial which is made after the notification of a decision referred to in Article 8 in at least one Member State concerned and which is likely to have a substantial impact on the safety or rights of the subject or on the reliability and robustness of data generated in the clinical trial;

(13a) ‘Parallel substantial modification’ means a substantial modification for which an application is submitted to a Member State concerned before a decision on a previous application for a substantial modification to the same clinical trial is notified by that Member State to the sponsor;

(14) ‘Sponsor’ means an individual, company, institution or organisation which takes responsibility for the initiation, for the management and for setting up the financing of the clinical trial;

(15) ‘Investigator’ means an individual responsible for the conduct of a clinical trial at a clinical trial site;

(16) ‘Principal investigator’ means an investigator who is the responsible leader of a team of investigators who conduct a clinical trial at a clinical trial site;

(17) ‘Subject’ means an individual who participates in a clinical trial, either

as recipient of an investigational medicinal product or as a control;

- (18) ‘Minor’ means a subject who is, according to the law of the Member State concerned, under the age of legal competence to give informed consent;
- (19) ‘Incapacitated subject’ means a subject who is, for reasons other than the age of legal competence to give informed consent, incapable of giving informed consent according to the law of the Member State concerned;
- (20) ‘Legally designated representative’ means a natural or legal person, authority or body which, according to the law of the Member State concerned, is empowered to give informed consent on behalf of a subject who is an incapacitated subject or a minor;
- ~~(21) ‘Informed consent’ means a subject’s free and voluntary expression of his or her willingness to participate in a particular clinical trial, after having been informed of all aspects of the clinical trial that are relevant to the subject’s decision to participate or, in case of minors and of incapacitated subjects, an authorisation or agreement from their legally designated representative to include them in the clinical trial;~~

(21) ‘Informed consent’ means a subject’s free and voluntary expression of his or her willingness to participate in a particular clinical trial, after having been informed of all aspects of the clinical trial that are relevant to the subject’s decision to participate or, in case of minors and of incapacitated subjects, an authorisation or agreement from their legally designated representative to include them in a clinical trial, including consent given through the use of electronic systems, methods and processes, and signed electronically in accordance with Union law or equivalent standards;

- (22) ‘Protocol’ means a document that describes the objectives, design, methodology, statistical considerations and organisation of a clinical trial. The term ‘protocol’ encompasses successive versions of the protocol and protocol modifications;
- (23) ‘Investigator’s brochure’ means a compilation of the clinical and non-clinical data on the investigational medicinal product or products which are relevant to the study of the product or products in humans;
- (24) ‘Manufacturing’ means total and partial manufacture, as well as the various processes of dividing up, packaging and labelling (including blinding);

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- (25) ‘Start of a clinical trial’ means the first act of recruitment of a potential subject for a specific clinical trial, unless defined differently in the protocol;
- (26) ‘End of a clinical trial’ means the last visit of the last subject, or at a later point in time as defined in the protocol;
- (27) ‘Early termination of a clinical trial’ means the premature end of a clinical trial due to any reason before the conditions specified in the protocol are complied with;
- (28) ‘Temporary halt of a clinical trial’ means an interruption not provided in the protocol of the conduct of a clinical trial by the sponsor with the intention of the sponsor to resume it;
- (29) ‘Suspension of a clinical trial’ means interruption of the conduct of a clinical trial by a Member State;
- (30) ‘Good clinical practice’ means a set of detailed ethical and scientific quality requirements for designing, conducting, performing, monitoring, auditing, recording, analysing and reporting clinical trials ensuring that the rights, safety and well-being of subjects are protected, and that the data generated in the clinical trial are reliable and robust;
- (31) ‘Inspection’ means the act by a competent authority of conducting an official review of documents, facilities, records, quality assurance arrangements, and any other resources that are deemed by the competent authority to be related to the clinical trial and that may be located at the clinical trial site at the sponsor's and/or contract research organisation's facilities, or at other establishments which the competent authority sees fit to inspect;
- (32) ‘Adverse event’ means 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;
- (33) ‘Serious adverse event’ means any untoward medical occurrence 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;
- (34) ‘Unexpected serious adverse reaction’ means a serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference safety information;

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- (35) 'Clinical study report' means a report on the clinical trial presented in an easily searchable format, prepared in accordance with Annex I, Part I, Module 5 of Directive 2001/83/EC and accompanying an application for marketing authorisation.
- (36) Consideration' means a justified concern or divergent view raised by a Member State concerned in the process of an assessment of an application for an authorisation of a clinical trial or for a substantial modification on the aspects that, if unresolved, will result in a negative decision on the clinical trial or substantial modification application;
- (37) 'Reporting Member State' means the Member State concerned that:
- (a) is responsible for the assessment and authorisation of the clinical trial application in mono-national clinical trials, or
 - (b) is leading the assessment for the authorisation of a multinational clinical trial or of a substantial modification regarding aspects covered by Part I of the application dossier, or
 - (c) is leading the assessment for the authorisation of a multinational combined study;
- (38) 'Investigational medicinal product core dossier' means a dossier, containing documents referred to in point (Ga), Part II of Annex I concerning the investigational medicinal product, established at the request of the sponsor in view of supporting the development of the investigational medicinal product.
- (39) 'Core dossier depositary Member State' means a Member State responsible for assessing suitability and completeness of the investigational medicinal product core dossier to be established and for the regulatory oversight of an already established dossier;
- (40) 'Core dossier competent Member States' means the Member States concerned for all corresponding clinical trials and the Member States indicated by a sponsor at the time of the initial request for the establishment of the investigational medicinal product core dossier;
- (41) 'Corresponding clinical trial' means a clinical trial tested to the investigational medicinal product for which an establishment of an investigational medicinal product core dossier has been requested and any subsequent clinical trial tested to that investigational medicinal product;

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- (42) **‘Distribution’ means all activities, consisting of procuring, holding, supplying, shipping across Member States or exporting investigational medicinal product or auxiliary medicinal products, , including delivery of investigational and auxiliary medicinal products to the clinical trial participants;**
- (43) **‘Direct delivery to the subject’ means controlled and documented direct delivery of an investigational medicinal product or an auxiliary medicinal product to the subject’s place of residence in a Member State, where the clinical trial has been authorised;**
- (44) **‘Combined study’ means a clinical trial concerning one or more medicinal products combined with a performance study of one or more in vitro diagnostic medical devices, as defined in Article 2 point (42) of Regulation (EU) 2017/746 of the European Parliament and of the Council* and/or clinical investigation of one or more medical devices as defined in Article 2 point (45) of Regulation (EU) 2017/745 of the European Parliament and of the Council **;**
- (45) **‘Regulatory sandbox’ means a regulatory framework that allows for the development and testing of innovative or adapted regulatory approaches in a controlled environment pursuant to a specific plan, for a limited time and under regulatory supervision, that enables innovation driven approaches to an authorisation and conduct of clinical trials that otherwise would not be possible or appropriate given current legal framework;’**
- (46) **‘AI system’ means AI system as defined in Article 3(1) of Regulation (EU) 2024/1689 of the European Parliament and of the Council***;**
- (47) **‘serious cross-border threat to health’ means serious cross-border threat to health as defined in Article 3(1) of Regulation (EU) 2022/2371 of the European Parliament and of the Council****.**

* Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU (JO 5.5.2017, L117/176., ELI: <http://data.europa.eu/eli/reg/2017/746/oj>).

** Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (JO 5.5.2017, L 117/1., ELI: <http://data.europa.eu/eli/reg/2017/745/oj>).

*** Regulation (EU) 2024/1689 of the European Parliament and of the Council of 13 June 2024 laying down harmonised rules on artificial intelligence and amending Regulations (EC) No 300/2008, (EU) No 167/2013, (EU) No 168/2013, (EU) 2018/858, (EU) 2018/1139 and (EU) 2019/2144 and Directives 2014/90/EU, (EU) 2016/797 and (EU) 2020/1828 (OJ L, 2024/1689, 12.7.2024, ELI: <http://data.europa.eu/eli/reg/2024/1689/oj>).

**** Regulation (EU) 2022/2371 of the European Parliament and of the Council of 23 November 2022 on serious cross-border threats to health and repealing Decision No 1082/2013/EU (OJ L 314, 6.12.2022, p. 26, <http://data.europa.eu/eli/reg/2022/2371/oj>).

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3. For the purposes of this Regulation, a subject who falls under the definition of both ‘minor’ and ‘incapacitated subject’ shall be deemed to be an incapacitated subject.

Article 3

General principle

1. ~~A clinical trial may be conducted only if:~~
2. ~~(a) the rights, safety, dignity and well-being of subjects are protected and prevail over all other interests; and~~
- ~~(b) it is designed to generate reliable and robust data.~~

General principles

- 1. A clinical trial may be conducted only if:**
- (a) the rights, safety, dignity and well-being of subjects are protected and prevail over all other interests; and**
- (b) it is designed to generate reliable and robust data.**
- 2. Member States concerned shall cooperate closely and efficiently to ensure the effective and timely application of the provisions of this Regulation.**
- 3. Member States shall take into account whether a clinical trial is a minimal-intervention or low-intervention clinical trial and, where this is the case, adapt the regulatory requirements throughout the lifecycle of such clinical trial, in particular with regard to the application dossier, the authorisation procedures, the safety reporting and oversight.**

CHAPTER II

AUTHORISATION PROCEDURE FOR A CLINICAL TRIAL

Article 4

Prior authorisation

~~A clinical trial shall be subject to scientific and ethical review and shall be authorised in accordance with this Regulation.~~

~~The ethical review shall be performed by an ethics committee in accordance with the law of the Member State concerned. The review by the ethics committee may~~

~~encompass aspects addressed in Part I of the assessment report for the authorisation of a clinical trial as referred to in Article 6 and in Part II of that assessment report as referred to in Article 7 as appropriate for each Member State concerned.~~

~~Member States shall ensure that the timelines and procedures for the review by the ethics committees are compatible with the timelines and procedures set out in this Regulation for the assessment of the application for authorisation of a clinical trial.~~

A clinical trial shall be conducted only if it has been authorised by the Member State concerned in accordance with this Regulation. Applications for an authorisation shall be subject to scientific and ethical review.

In clinical trials concerning more than one Member States (multinational clinical trials) all the Member States concerned including the reporting Member State shall cooperate in good faith and in spirit of mutual trust and reliance. The reporting Member State shall have a leading role in the assessments.

The ethical review shall be performed by an ethics committee in accordance with the law of the Member State concerned. The reporting Member State shall involve its ethics committee in the assessment of ethical aspects of Part I of the application dossier referred to in Article 6.

Each Member State shall ensure that the organisation, timelines and procedures for the review by an ethics committee are compatible with the timelines and procedures set out in this Regulation for the assessment of the application for authorisation of a clinical trial and substantial modifications thereof.

Article 5 Submission of an application

~~1. In order to obtain an authorisation, the sponsor shall submit an application dossier to the intended Member States concerned through the portal referred to in Article 80 (the ‘EU portal’).~~

~~The sponsor shall propose one of the Member States concerned as reporting Member State.~~

~~If a Member State concerned other than the proposed reporting Member State is willing to be the reporting Member State or where the proposed reporting Member State does not wish to be the reporting Member State, this shall be notified through the EU portal to all Member States concerned not later than three days after the application dossier is submitted.~~

~~If only one Member State concerned is willing to be the reporting Member State or if the clinical trial involves only one Member State, that Member State shall be the reporting Member State.~~

~~If there is no Member State concerned willing to be the reporting Member State or if there is more than one Member State concerned willing to be the reporting Member State, the reporting Member State shall be selected by agreement among the Member States concerned taking into account the recommendations referred to in point (c) of Article 85(2).~~

~~If there is no agreement among the Member States concerned, the proposed reporting Member State shall be the reporting Member State.~~

~~The reporting Member State shall notify the sponsor and the other Member States concerned that it is the reporting Member State, through the EU portal, within six days from the submission of the application dossier.~~

~~2. The sponsor shall, when applying for a low-intervention clinical trial, where the investigational medicinal product is not used in accordance with the terms of the marketing authorisation but the use of that product is evidence-based and supported by published scientific evidence on the safety and efficacy of that product, propose one of the Member States concerned where the use is evidence-based, as reporting Member State.~~

~~3. Within 10 days from the submission of the application dossier, the reporting Member State shall validate the application taking into account considerations expressed by the other Member States concerned and notify the sponsor, through the EU portal, of the following:~~

~~(a) whether the clinical trial applied for falls within the scope of this Regulation;~~

~~(b) whether the application dossier is complete in accordance with Annex I;~~

~~Member States concerned may communicate to the reporting Member State any considerations relevant to the validation of the application within seven days from the submission of the application dossier.~~

~~4. Where the reporting Member State has not notified the sponsor within the period referred to in the first sub-paragraph of paragraph 3, the clinical trial applied for shall be deemed to fall within the scope of this Regulation and the application dossier shall be considered complete.~~

~~5. Where the reporting Member State, taking into account considerations expressed by the other Member States concerned, finds that the application dossier is not complete, or that the clinical trial applied for does not fall within the scope of this Regulation, it shall inform the sponsor thereof through the EU portal and shall set a maximum of 10 days for the sponsor to comment on the application or to complete the application dossier through the EU portal.~~

~~Within five days from receipt of the comments or the completed application dossier, the reporting Member State shall notify the sponsor as to whether or not the application complies with the requirements set out in points (a) and (b) of the first subparagraph of paragraph 3.~~

~~Where the reporting Member State has not notified the sponsor within the period referred to in the second subparagraph, the clinical trial applied for shall be deemed to fall within the scope of this Regulation and the application dossier shall be considered complete.~~

~~Where the sponsor has not provided comments or completed the application dossier within the period referred to in the first subparagraph, the application shall be deemed to have lapsed in all Member States concerned.~~

~~6. For the purposes of this Chapter, the date on which the sponsor is notified in accordance with paragraph 3 or 5 shall be the validation date of the application. Where the sponsor is not notified, the validation date shall be the last day of the respective periods referred to in paragraphs 3 and 5.~~

1. In order to obtain an authorisation, the sponsor shall submit an application dossier to the intended Member States concerned throughout the Portal referred to in Article 80 ('the EU portal') referred to in Article 25. The date on which the sponsor submits the application for an authorisation of a clinical trial is referred to within this Chapter as the submission date.

2. The authorisation procedure of a clinical trial consists of three steps:

(a) a validation of the application dossier, as set out in Article 5b;

(b) an assessment, that consists of:

- an assessment of Part I, as set out in Article 6, of the elements of the application dossier listed in Part I of Annex I, that constitute Part I of the assessment dossier, and

- an assessment of Part II, as set out Article 7 of the application dossier, of the elements listed in Part II of Annex I, that constitute Part II of the application dossier.

(c) a decision resulting either an authorisation, conditional authorisation or refusal of an authorisation, as set out in Article 8.²

Article 5a*

Appointment of the reporting Member State

- 1. In clinical trials concerning only one Member State, this Member State is the reporting Member State.**
- 2. In clinical trials concerning more than one Member States, the sponsor shall propose one of the Member States concerned as the reporting Member State. All Member States concerned willing to become the reporting Member State shall declare their willingness through the EU portal.**

The sponsor shall, when applying for a low-intervention clinical trial propose one of the Member States concerned where the use of the investigational medicinal product is evidence-based as a reporting Member State.
- 3. If the proposed Member State accepts the proposal by expressing willingness to become the reporting Member State, it shall be the reporting Member State.**
- 4. If the proposed Member State does not accept the proposal, the following rules shall apply, and their application shall be supported by the EU Portal:**
 - (a) where there is only one other Member State concerned willing to become the reporting Member State, that Member State shall become the reporting Member State;**
 - (b) where there is more than one Member State concerned willing to become the reporting Member State or none of the Member States concerned is willing to become the reporting Member State, the reporting Member State shall be designated automatically by the EU Portal in application of the recommendation referred to in article 85(2)(c).**
- 5. Within three days from the submission date, all Member States concerned, the sponsor and the reporting Member State shall be notified by the EU Portal of the appointment of the reporting Member State.**

* NB: The Regulation of the European Parliament and the Council laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006 introduces a new Article 5a. Following the adoption and entry into force of that Regulation, Articles 5a and 5b should become Articles 5b and 5c, respectively.

Article 5b

Validation of Part I of the application dossier

1. Within seven days from the submission date, the reporting Member State shall validate Part I of application dossier referred to in Article 6 and notify the sponsor, through the EU portal, of the following:

 - (a) whether the clinical trial applied for falls within the scope of this Regulation;
 - (b) whether the application dossier is complete in accordance with Part I of Annex I;
 - (c) whether it confirms that the clinical trial is a minimal-intervention or a low-intervention clinical trial, respectively, if such a claim was made by the sponsor.
2. Where the reporting Member State has not notified the sponsor within the period referred to in paragraph 1, the clinical trial applied for shall be deemed to fall within the scope of this Regulation and the application dossier shall be considered complete and, if applicable, the clinical trial shall be considered a minimal-intervention or low-intervention clinical trial.
3. Where the reporting Member State finds that the application dossier is not complete, or that the clinical trial applied for does not fall within the scope of this Regulation, or, if applicable, has doubts whether the clinical trial is a minimal-intervention or low-intervention clinical trial, the reporting Member State shall:

 - (a) inform the sponsor thereof through the EU portal and shall set a deadline of maximum seven days for the sponsor to comment on the application or to complete the application dossier through the EU portal;
 - (b) within seven days from the submission of the comments or the completed application dossier referred to in point (a) notify the sponsor as to whether or not the application complies with the requirements set out in paragraph 1 points (a), (b) and (c).

In case the reporting Member State requests the sponsor to comment on the application pursuant to this paragraph, the period referred to in paragraph 1 may be extended by a maximum of 14 days.
4. Where the reporting Member State has not notified the sponsor within the period referred to in paragraph 3, point (b), the clinical trial applied for shall be deemed to fall within the scope of this Regulation, the application dossier shall be considered complete in accordance with Part I of Annex I and the clinical trials is deemed to be a minimal-intervention or a low-intervention clinical trial, if claimed by the sponsor.
5. Where the sponsor has not provided comments or completed the application dossier within the period referred to in paragraph 3, point (a),

the application shall be deemed to have lapsed in all Member States concerned.

- 6. For the purpose of this Chapter, the date on which the sponsor is notified in accordance with paragraph 1 or paragraph 3, point (b) shall be the validation date of the application. Where the sponsor is not notified within these time periods, the validation date shall be the last day of respective periods referred to in paragraph 1 or paragraph 3, point (b).**

Article 6

Assessment report — Aspects covered by Part I of the assessment report

- ~~1. The reporting Member State shall assess the application with regard to the following aspects:~~
 - ~~(a) Whether the clinical trial is a low-intervention clinical trial, where claimed by the sponsor;~~
 - ~~(b) Compliance with Chapter V with respect to the following:
 - ~~(i) The anticipated therapeutic and public health benefits taking account of all of the following:
 - ~~— the characteristics of and knowledge about the investigational medicinal products;~~
 - ~~— the relevance of the clinical trial, including whether the groups of subjects participating in the clinical trial represent the population to be treated, or if not, the explanation and justification provided in accordance with point (y) of paragraph 17 of Annex I to this Regulation; the current state of scientific knowledge; whether the clinical trial has been recommended or imposed by regulatory authorities in charge of the assessment and authorisation of the placing on the market of medicinal products; and, where applicable, any opinion formulated by the Paediatric Committee on a paediatric investigation plan in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council⁽¹⁾;~~
 - ~~— the reliability and robustness of the data generated in the clinical trial, taking account of statistical approaches, design of the clinical trial and methodology, including sample size and randomisation, comparator and endpoints;~~~~
 - ~~(ii) The risks and inconveniences for the subject, taking account of all of the following:
 - ~~— the characteristics of and knowledge about the investigational medicinal products and the auxiliary medicinal products;~~
 - ~~— the characteristics of the intervention compared to normal clinical practice;~~
 - ~~— the safety measures, including provisions for risk minimisation measures, monitoring, safety reporting, and the safety plan;~~~~~~

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- ~~—the risk to subject health posed by the medical condition for which the investigational medicinal product is being investigated;~~
- ~~(c) Compliance with the requirements concerning the manufacturing and import of investigational medicinal products and auxiliary medicinal products set out in Chapter IX;~~
 - ~~(d) Compliance with the labelling requirements set out in Chapter X;~~
 - ~~(e) The completeness and adequateness of the investigator's brochure.~~
- ~~2. The reporting Member State shall draw up an assessment report. The assessment of the aspects referred to in paragraph 1 shall constitute Part I of the assessment report.~~
- ~~3. The assessment report shall contain one of the following conclusions concerning the aspects addressed in Part I of the assessment report:~~
- ~~(a) the conduct of the clinical trial is acceptable in view of the requirements set out in this Regulation;~~
 - ~~(b) the conduct of the clinical trial is acceptable in view of the requirements set out in this Regulation, but subject to compliance with specific conditions which shall be specifically listed in that conclusion; or~~
 - ~~(c) the conduct of the clinical trial is not acceptable in view of the requirements set out in this Regulation.~~
- ~~4. The reporting Member State shall submit, through the EU portal, the final Part I of the assessment report, including its conclusion, to the sponsor and to the other Member States concerned within 45 days from the validation date.~~
- ~~5. For clinical trials involving more than one Member State, the assessment process shall include three phases:~~
- ~~(a) an initial assessment phase performed by the reporting Member State within 26 days from the validation date;~~
 - ~~(b) a coordinated review phase performed within 12 days from the end of the initial assessment phase involving all Member States concerned;~~
 - ~~(c) a consolidation phase performed by the reporting Member State within seven days from the end of coordinated review phase.~~

~~During the initial assessment phase, the reporting Member State shall develop a draft Part I of the assessment report and circulate it to all other Member States concerned.~~

~~During the coordinated review phase, all Member States concerned shall jointly review the application based on the draft Part I of the assessment report and shall share any considerations relevant to the application.~~

~~During the consolidation phase, the reporting Member State shall take due~~

account of the considerations of the other Member States concerned when finalising Part I of the assessment report and shall record how all such considerations have been dealt with. The reporting Member State shall submit the final Part I of the assessment report to the sponsor and all other Member States concerned within the period referred to in paragraph 4.

6. For the purposes of this Chapter, the date on which the final Part I of the assessment report is submitted by the reporting Member State to the sponsor and to the other Member States concerned shall be the reporting date.
7. The reporting Member State may also extend the period referred to in paragraph 4 by a further 50 days for clinical trials involving an advanced therapy investigational medicinal products or a medicinal product as defined in point 1 of the Annex to Regulation (EC) No 726/2004, for the purpose of consulting with experts. In such case, the periods referred to in paragraphs 5 and 8 of this Article shall apply *mutatis mutandis*.
8. Between the validation date and the reporting date, only the reporting Member State may request additional information from the sponsor, taking into account the considerations referred to in paragraph 5.

For the purpose of obtaining and reviewing this additional information from the sponsor in accordance with the third and fourth subparagraph, the reporting Member State may extend the period referred to in paragraph 4 by a maximum of 31 days.

The sponsor shall submit the requested additional information within the period set by the reporting Member State which shall not exceed 12 days from the receipt of the request.

Upon receipt of the additional information, the Member States concerned shall jointly review any additional information provided by the sponsor together with the original application and shall share any considerations relevant to the application. The coordinated review shall be performed within a maximum of 12 days of the receipt of the additional information and the further consolidation shall be performed within a maximum of seven days of the end of coordinated review. When finalising Part I of the assessment report, the reporting Member State shall take due account of the considerations of the Member States concerned and shall record how all such considerations have been dealt with.

Where the sponsor does not provide additional information within the period set by the reporting Member State in accordance with the third subparagraph, the application shall be deemed to have lapsed in all Member States concerned.

The request for additional information and the additional information shall be submitted through the EU portal.

1. The reporting Member State shall assess the application relying on the information and the documents listed in Part I of Annex I, with regard to the following aspects:

(a) compliance with Chapter V as with respect to the following:

(i) the anticipated therapeutic and public health benefits taking account of all of the following:

- characteristic of and knowledge about the investigational medicinal products;**
- relevance of the clinical trial, including whether the groups of subjects participating in the clinical trial represent the population to be treated, or if not, the explanation and justification provided in accordance with point 17(y) of Part I of Annex I; the current state of scientific knowledge; whether the clinical trial has been recommended or imposed by regulatory authorities in charge of the assessment and authorisation of the placing on the market of medicinal products; where applicable, taking into account any opinion formulated by the Paediatric Committee on paediatric investigational plan in accordance with Chapter VII of Regulation (EU) .../... [reference to be added after adoption cf. COM(2023)196final];**
- reliability and robustness of the data generated in clinical trial, taking into account of statistical approaches, design of the clinical trial and methodology, including sample size and randomisation, comparator and endpoints;**

(ii) risk and inconveniences for the subjects, taking into account all of the following:

- characteristic of and knowledge about the investigational medicinal product and the auxiliary medicinal product;**
- characteristic of the investigational medicinal product;**
- safety measures, including provisions for risk minimisation measures, monitoring, safety reporting, and the safety plan;**
- risk to subjects' health posed by the medical condition for which the investigational medicinal product is being investigated;**
- aspects related to the protection of the subjects' safety, well-being**

and fundamental rights as a clinical trial participant.

(b) compliance with the requirements concerning the manufacturing and import of investigational medicinal product set out in Chapter IX;

(c) compliance with the labelling requirements set out in Chapter X;

(d) completeness and adequacy of the investigator's brochure.

The adequacy of the translations of the documents, when translations are required pursuant to Article 26 and Article 69, submitted in Part I shall be assessed in Part II.

2. The reporting Member State shall draw up an assessment report. The assessment of the aspects referred to in paragraph 1 shall constitute Part I of the assessment report.

The ethics committee of the reporting Member State shall review, from the ethical perspective, aspects covered by Part I of the assessment report. That ethical review shall complement the scientific and regulatory assessment and shall cover Part I of the application dossier in order to evaluate whether the subjects' rights, safety and well-being are being ensured in the clinical trial.

2a. Notwithstanding paragraph 2, where the clinical trial is a minimal-intervention clinical trial, the assessment of the reporting Member State shall be limited to an ethical review by its ethics committee of the aspects referred to points (a) and (d) of paragraph 1.

3. The assessment report shall contain one of the following conclusions concerning the aspects addressed in Part I of the assessment report:

(a) the conduct of the clinical trial is acceptable in view of the requirements set out in this Regulation:

(b) the conduct of the clinical trial is acceptable in view of the requirements set out in this Regulation, but subject to compliance with specific conditions which shall be specifically listed in that conclusion; or

(c) the conduct of the clinical trial is not acceptable in view of the requirements set out in this Regulation.

4. The reporting Member state shall submit, through EU portal, the final Part I of the assessment report, including its conclusions, to the sponsors and to the other Member States concerned within 42 days from the submission date.

5. For clinical trials involving more than one Member State concerned, the assessment process shall include three phases:

(a) an initial assessment phase within 28 days from the submission date;

(b) a review phase within seven days from the end of the initial assessment;

(c) a consolidation phase within seven days from the end date of the review phase.

During the initial assessment phase, the reporting Member State shall assess Part I of the application dossier and draw up a draft Part I of the assessment report and circulate it to all other Member States concerned within 28 days from the submission date.

During the review phase, within seven days from the circulation of the draft assessment report all Member States concerned shall review the application based on the draft Part I of the assessment report and shall share considerations for their Member States relevant to the application. The consideration may be raised only on one of the following grounds:

(a) one of the grounds referred to in Article 8(2);

(b) issues that would lead to a negative opinion of the ethics committee of the Member State concerned.

During the consolidation phase, the reporting Member State shall take due account of the considerations of the other Member States concerned and finalise Part I of the assessment report and shall record how all considerations have been dealt with. The reporting Member State shall submit the final Part I of the assessment report to the sponsor and all other Member States concerned within seven days from the end of the review phase.

5a. Where the clinical trial is a minimal-intervention clinical trial, other Member States concerned may only raise during the review phase considerations referred to in paragraph 5 related to ethical aspects of the draft assessment report.

6. For the purpose of this Chapter, the date on which the final Part I of the assessment report is submitted by the reporting Member State to the sponsor and to the other Member States concerned through the EU portal shall be the

reporting date.

7. Between the validation date and the reporting date, only the reporting Member State may request additional information from the sponsor, taking into account the considerations referred to in paragraph 5.

For the purpose of obtaining and reviewing this additional information from the sponsor, the reporting Member State may extend the period referred to in paragraph 4 by maximum of 28 days.

The sponsor shall submit the requested information within the period set by the reporting Member State which shall not exceed 14 days from the receipt of the request.

Upon receipt of the requested additional information, the Member State concerned shall review additional information provided by the sponsor and shall identify and share with the reporting Member State any unaddressed considerations, relevant for the application. The coordinated review shall be performed within maximum 7 days of the receipt of the additional information and the further consolidation shall be performed within maximum seven days of the end of the coordinated review. When finalising Part I of the assessment report, the reporting Member State shall take due account of the considerations of the other Member States concerned and shall record how the considerations have been dealt with.

Where the sponsor does not provide additional information within the period set by the reporting Member State in accordance with the third subparagraph, the application shall be deemed to have lapsed in all Member States concerned.

The request for additional information and additional information shall be submitted through the EU Portal.

Article 7

Assessment report — Aspects covered by Part II of the application dossier

~~1. Each Member State concerned shall assess, for its own territory, the application with respect to the following aspects:~~

~~(a) compliance with the requirements for informed consent as set out in Chapter V;~~

~~(b) compliance of the arrangements for rewarding or compensating subjects with the requirements set out in Chapter V and investigators;~~

~~(c) compliance of the arrangements for recruitment of subjects with the requirements set out in Chapter V;~~

~~(d) compliance with Directive 95/46/EC;~~

~~(e) compliance with Article 49;~~

~~(f) compliance with Article 50;~~

~~(g) compliance with Article 76;~~

~~(h) compliance with the applicable rules for the collection, storage and future use of~~

~~biological samples of the subject. The assessment of the aspects referred to in the first subparagraph shall constitute Part II of the assessment report.~~

~~2. Each Member State concerned shall complete its assessment within 45 days from the validation date and submit, through the EU portal, Part II of the assessment report, including its conclusion, to the sponsor.~~

~~Each Member State concerned may request, with justified reasons, additional information from the sponsor regarding the aspects referred to in paragraph 1 only within the period referred to in the first subparagraph.~~

~~3. For the purpose of obtaining and reviewing the additional information referred to in the second subparagraph of paragraph 2 from the sponsor in accordance with the second and third subparagraph, the Member State concerned may extend the period referred to in the first subparagraph of paragraph 2 by a maximum of 31 days.~~

~~The sponsor shall submit the requested additional information within the period set by the Member State concerned which shall not exceed 12 days from the receipt of the request.~~

~~Upon receipt of the additional information, the Member State concerned shall complete its assessment within a maximum of 19 days.~~

~~Where the sponsor does not provide additional information within the period set by the Member State concerned in accordance with the second subparagraph, the application shall be deemed to have lapsed in that Member State concerned.~~

~~The request for additional information and the additional information shall be submitted through the EU portal.~~

1. Each Member State concerned shall assess, for its own territory, the application with respect to the following aspects. Such assessment shall constitute Part II of the assessment report:

(a) compliance with the requirements for informed consent set out in Chapter V;

-
- (b) compliance of the arrangements for rewarding or compensating subjects with the requirements set out in Chapter V;**
 - (c) compliance of the arrangements for recruitment of subjects with the requirements set out in Chapter V;**
 - (d) compliance with Regulation (EU) 2016/679 of the European Parliament and of the Council*;**
 - (e) compliance with Article 49;**
 - (f) compliance with Article 50;**
 - (g) compliance with Article 76;**
 - (h) compliance with applicable rules for the collection, storage and future use of biological samples of the subject;**
 - (i) accuracy of the translations of the documents and information submitted in Part I of the application dossier, when such documents are required to be submitted in the national language in accordance with Article 26 and 69.**

2. Each Member State concerned shall complete the assessment within 42 days from the submission date and submit, through the EU portal, Part II of the assessment report, including its conclusions, to the sponsor.

Each Member State concerned may within the period referred to in this paragraph, and through EU portal, request on duly justified grounds additional information, from the sponsor regarding the aspects covered in paragraph 1 or to request to complement the documentation, required pursuant to Part II of Annex I, if such documentation is missing or documentation provided is not adequate or is incomplete.

The Member State concerned may decide within 28 days of the submission date to rely on the ethical review of the ethics committee of the reporting Member State of the common elements of the application dossier of Part II and inform the sponsor accordingly.

3. Each Member State concerned may extend the assessment period referred to in paragraph 2 by a maximum of 28 days:

(a) to requests additional documentation or information, as referred in paragraph 2, from the sponsor regarding Part II of the assessment for its territory;

(b) to align with the timeline for the assessment referred to in Article 6, when it has been extended to allow for a request for information by the reporting Member State related to Part I assessment and its review.

The sponsor shall submit the requested additional information and

* * Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation), OJ L 119, 4.5.2016., ELI: <http://data.europa.eu/eli/reg/2016/679/oj>.

documentation within the period set by the Member State concerned which shall not exceed 14 days from the receipt of the request.

Upon receipt of the additional information and documentation, the Member State concerned shall complete its assessment within maximum of 14 days from the submission of the requested information by the sponsor.

Where the sponsor does not provide additional information and documentation within the period set by the Member State concerned in accordance with this paragraph, the application shall be deemed to have lapsed in that Member State concerned.

Article 8

Decision on the clinical trial

~~1. Each Member State concerned shall notify the sponsor through the EU portal as to whether the clinical trial is authorised, whether it is authorised subject to conditions, or whether authorisation is refused.~~

~~Notification shall be done by way of one single decision within five days from the reporting date or from the last day of the assessment referred to in Article 7, whichever is later.~~

~~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.~~

1. Each Member State concerned shall notify the sponsor through the EU portal and by way of one single decision as to whether the clinical trial is authorised, authorised subject to conditions, or whether authorisation is refused.

The notification shall be made within five days from the reporting date or from the last day of the assessment referred to in Article 7, whichever is later.

~~2. Where the conclusion of the reporting Member State as regards Part I of the assessment report is that the conduct of the clinical trial is acceptable or acceptable subject to compliance with specific conditions, that conclusion shall be deemed to be the conclusion of the Member State concerned.~~

~~Notwithstanding the first subparagraph, a Member State concerned may disagree with the conclusion of the reporting Member State as regards Part I of the assessment report only on the following grounds:~~

~~(a) when it considers that participation in the clinical trial would lead to a subject receiving an inferior treatment than in normal clinical practice in the Member State concerned;~~

~~(b) infringement of its national law as referred to in Article 90;~~

~~(c) considerations as regards subject safety and data reliability and robustness submitted under paragraph 5 or 8 of Article 6.~~

~~Where a Member State concerned disagrees with the conclusion on the basis of the second subparagraph, it shall communicate its disagreement, together with a detailed justification, through the EU portal, to the Commission, to all Member States, and to the sponsor.~~

2. Where the conclusion of the reporting Member State as regards Part I of the assessment report is that the conduct of the clinical trial is acceptable or acceptable subject to compliance with specific conditions, that conclusion shall be deemed to be the conclusion of the Member States concerned.

A clinical trial subject to conditions may start, unless the Member State concerned specified that the condition is suspensive. Unless otherwise specified, a fulfilment of the condition shall not require a submission of a request for a substantial modification.

Notwithstanding the first subparagraph of this paragraph, a Member State concerned may disagree with the conclusion of the reporting Member State as regards Part I of the assessment report only on the following grounds, provided that the corresponding consideration was raised during the process pursuant to Article 6(5) point (b) and the Member State concerned considers that it was not sufficiently addressed.

(a) participation in the clinical trial would lead to a subject receiving an inferior treatment than in normal clinical practice in the Member State concerned; or

(b) infringement of its national law as referred to in Article 90.

Where a Member State concerned disagrees with the conclusion, it shall communicate its disagreement, together with a detailed justification, through the EU portal, to the Commission, to all Member States, and to the sponsor.

3. Where, regarding the aspects covered by Part I of the assessment report, the clinical trial is acceptable or acceptable subject to compliance with specific conditions, the Member State concerned shall include in its decision its conclusion on Part II of the assessment report.

4. A Member State concerned shall refuse to authorise a clinical trial if it disagrees with the conclusion of the reporting Member State as regards Part I of the assessment report on any of the grounds referred to in the second subparagraph of paragraph 2, or if it finds, on duly justified grounds, that the aspects addressed in Part II of the assessment report are not complied with, or where an ethics committee has issued a negative opinion which in accordance with the law of the Member State concerned is valid for that entire Member State. That Member State shall provide for an appeal procedure in respect of such refusal.

5. Where the conclusion of the reporting Member State as regards Part I of the

assessment report is that the clinical trial is not acceptable, that conclusion shall be deemed to be the conclusion of all Member States concerned.

6. Where the Member State concerned has not notified the sponsor of its decision within the relevant periods referred to in paragraph 1, the conclusion on Part I of the assessment report shall be deemed to be the decision of the Member State concerned on the application for authorisation of the clinical trial.

7. The Member States concerned shall not request additional information regarding the aspects addressed in Part I of the assessment report from the sponsor after the reporting date.

8. For the purposes of this Chapter, the notification date shall be the date on which the decision referred to in paragraph 1 is notified to the sponsor. Where the sponsor has not been notified in accordance with paragraph 1, the notification date shall be deemed to be the last day of the period provided for in paragraph 1.

9. If no subject has been included in the clinical trial in a Member State concerned within two years from the notification date of the authorisation, the authorisation shall expire in that Member State concerned unless an extension, on request of the sponsor, has been approved following the procedure set out in Chapter III.

Article 9

Persons assessing the application

~~1. Member States shall ensure that the persons validating and assessing the application do not have conflicts of interest, are independent of the sponsor, of the clinical trial site and the investigators involved and of persons financing the clinical trial, as well as free of any other undue influence.~~

~~In order to guarantee independence and transparency, the Member States shall ensure that persons admitting and assessing the application as regards the aspects addressed in Parts I and II of the assessment report have no financial or personal interests which could affect their impartiality. These persons shall make an annual declaration of their financial interests.~~

~~2. Member States shall ensure that the assessment is done jointly by a reasonable number of persons who collectively have the necessary qualifications and experience.~~

~~3. At least one layperson shall participate in the assessment.~~

1. Member States shall ensure, including through the institutional safeguards, that persons validating and assessing the application do not have conflicts of interest, are independent of the sponsors, or the clinical trial site

and the investigators involved and of persons financing the clinical trial, as well as free of any other undue influence and ensure their sufficient independence in performance of their tasks.

In order to guarantee independency and transparency, the Member States shall ensure that persons validating and assessing the application as regards the aspects covered in Parts I and II of the assessment report have no financial or personal interests which could affect their impartiality. These persons shall make an annual declaration of their financial interest.

2. Member States shall ensure that the assessment is done by persons who collectively have the necessary qualifications and experience.

These persons shall be sufficiently equipped and empowered to perform their tasks.

3. At least one layperson shall participate in the assessment

Article 10

Specific considerations for vulnerable populations

1. Where the subjects are minors, specific consideration shall be given to the assessment of the application for authorisation of a clinical trial on the basis of paediatric expertise or after taking advice on clinical, ethical and psycho- social problems in the field of paediatrics
2. Where the subjects are incapacitated subjects, specific consideration shall be given to the assessment of the application for authorisation of a clinical trial on the basis of expertise in the relevant disease and the patient population concerned or after taking advice on clinical, ethical and psychosocial questions in the field of the relevant disease and the patient population concerned.
3. Where the subjects are pregnant or breastfeeding women, specific consideration shall be given to the assessment of the application for authorisation of a clinical trial on the basis of expertise in the relevant condition and the population represented by the subject concerned.
4. If according to the protocol a clinical trial provides for the participation of specific groups or subgroups of subjects, where appropriate, specific consideration shall be given to the assessment of the application for authorisation of that clinical trial on the basis of expertise in the population represented by the subjects concerned.
5. In any application for authorisation of a clinical trial referred to in Article 35, specific consideration shall be given to the circumstances of the conduct of the clinical trial.
6. **Where potential subjects of a clinical trial belong to vulnerable populations,**

Member States concerned and sponsors shall consider and weigh the harms and benefits of their inclusion as opposed to their exclusion from a clinical trial. The Member States concerned and sponsors shall assess in particular whether the exclusion of those subjects from a clinical trial could inadvertently perpetuate or exacerbate their vulnerabilities, particularly in relation to their specific health needs.

Article 11

Submission and assessment of applications limited to aspects covered by Part I ~~or Part II~~ of the assessment report

~~Where the sponsor so requests, the application for authorisation of a clinical trial, its assessment and the conclusion shall be limited to the aspects covered by Part I of the assessment report.~~

~~After the notification of the conclusion on the aspects covered by Part I of the assessment report, the sponsor may within two years apply for an authorisation limited to aspects covered by Part II of the assessment report. In that application the sponsor shall declare that he is not aware of any new substantial scientific information that would change the validity of any item submitted in the application on the aspects covered by Part I of the assessment report. In this case, that application shall be assessed in accordance with Article 7 and the Member State concerned shall notify its decision on the clinical trial in accordance with Article 8. In those Member States where the sponsor does not apply for an authorisation limited to aspects covered by Part II of the assessment report within two years, the application on the aspects covered by Part I of the assessment report shall be deemed to have lapsed.~~

1. Where the sponsor so requests, the application for authorisation of a clinical trial, its assessment and the conclusion shall be limited to the aspects covered by Part I of the assessment report.

After the notification of the conclusion on the aspects covered by Part I of the assessment report, the sponsor may, within two years, apply for an authorisation limited to aspects covered by Part II of the assessment report.

Where the sponsor submits only Part I of the application dossier to all of the Member States concerned, the sponsor shall declare at the time of the first submission of Part II of the application dossier to any of the Member States concerned that the sponsor is not aware of any new substantial scientific information that would change the validity of any item submitted in the application on the aspects covered by Part I of the assessment report. If an update of Part I of the application dossier is necessary, the sponsor shall submit a substantial modification of Part I of the application dossier, at the latest, at the same time as the submission of Part II of the application dossier to at least one of the Member States concerned.

The Part II of the application dossier shall be assessed in accordance with Article 7 and the Member State concerned shall notify the decision on clinical trial in accordance with Article 8.

In those Member States concerned where the sponsor does not apply for an authorisation limited to aspects covered by Part II of the assessment report within two years, the application on the aspects covered by Part I of the assessment report shall be deemed to have lapsed.

2. When the sponsor submits a substantial modification of Part I of the application dossier with regard to clinical trial that is subject to a request referred to in paragraph 1 and has been authorised or authorised subject to conditions by at least one Member State concerned, all Member States concerned that received the initial application shall participate in the assessment of that substantial modification in accordance with Article 18 or 22 as appropriate.

Article 12
Withdrawal

The sponsor may withdraw the application at any time until the reporting date. In such a case, the application may only be withdrawn with respect to all Member States concerned. The reasons for the withdrawal shall be communicated through the EU portal.

Article 13
Resubmission

This Chapter is without prejudice to the possibility for the sponsor to resubmit, following the refusal to grant an authorisation or the withdrawal of an application, an application for authorisation to any intended Member State concerned. That application shall be deemed to be a new application for authorisation of another clinical trial.

Article 14
Subsequent addition of a Member State concerned

- ~~1. Where the sponsor wishes to extend an authorised clinical trial to another Member State ('additional Member State concerned'), the sponsor shall submit an application dossier to that Member State through the EU portal.~~

~~The application dossier may be submitted only after the notification date of the initial authorisation decision.~~

Where the sponsor wishes to extend an authorised clinical trial to another Member State (additional Member State concerned), the sponsor shall submit an application dossier to that Member State through the EU portal.

The application dossier may be submitted only after the notification date of the first initial authorisation decision by at least one Member State concerned.

2. The reporting Member State for the application dossier referred to in paragraph 1 shall be the reporting Member State for the initial authorisation procedure
3. ~~The additional Member State concerned shall notify the sponsor through the EU portal, within 52 days from the date of submission of the application dossier referred to in paragraph 1, by way of one single decision as to whether the clinical trial is authorised, whether it is authorised subject to conditions, or whether the authorisation is refused.~~

~~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.~~

3. The additional Member State concerned shall notify the sponsor, through the EU portal, within 47 days from the date of submission of the application dossier referred to in paragraph 1 of this Article, by way of one single decision as to whether the clinical trial is authorised, whether it is authorised subject to conditions, or whether the authorisation is refused. Article 8(2), (3), (4) and (5) apply to the decision of the additional Member State concerned.

4. ~~Where the conclusion of the reporting Member State as regards Part I of the assessment report is that the conduct of the clinical trial is acceptable or acceptable subject to compliance with specific conditions, that conclusion shall be deemed to be the conclusion of the additional Member State concerned.~~

~~Notwithstanding the first subparagraph, an additional Member State concerned may disagree with the conclusion of the reporting Member State as regards Part I of the assessment report only on the following grounds:~~

- (a) ~~when it considers that participation in the clinical trial would lead to a subject receiving an inferior treatment than in normal clinical practice in the Member State concerned;~~
- (b) ~~infringement of its national law as referred to in Article 90;~~
- (c) ~~considerations as regards subject safety and data reliability and robustness submitted under paragraph 5 or 6.~~

~~Where an additional Member State concerned disagrees with the conclusion on the basis of the second subparagraph, it shall communicate its disagreement, together with a detailed justification, through the EU portal, to the Commission, to all~~

Member States, and to the sponsor.

- ~~5. Between the date of submission of the application dossier referred to in paragraph 1 and five days before the expiry of the period referred to in paragraph 3, the additional Member State concerned may communicate to the reporting Member State and the other Member States concerned any considerations relevant to the application through the EU portal.~~
6. Within 42 days following the submission date referred to in paragraph 1, the additional Member State concerned may communicate to the reporting Member State and the other Member States concerned any considerations through the EU portal.
- ~~7. Between the date of submission of the application dossier referred to in paragraph 1 and the expiry of the period referred to in paragraph 3, only the reporting Member State may request additional information from the sponsor concerning the aspects addressed in Part I of the assessment report, taking into account the considerations referred to in paragraph 5.~~

~~For the purpose of obtaining and reviewing this additional information from the sponsor in accordance with the third and fourth subparagraphs, the reporting Member State may extend the period referred to in the first subparagraph of paragraph 3 by a maximum of 31 days.~~

~~The sponsor shall submit the requested additional information within the period set by the reporting Member State which shall not exceed 12 days from receipt of the request.~~

~~Upon receipt of the additional information, the additional Member State concerned together with all other Member States concerned shall jointly review any additional information provided by the sponsor together with the original application and shall share any considerations relevant to the application. The coordinated review shall be performed within a maximum of 12 days from the receipt of the additional information and the further consolidation shall be performed within a maximum of seven days from the end of the coordinated review. The reporting Member State shall take due account of the considerations of the Member States concerned and shall record how all such considerations have been dealt with.~~

~~Where the sponsor does not provide additional information within the period set by the reporting Member State in accordance with the third subparagraph, the application shall be deemed to have lapsed in the additional Member State concerned.~~

~~The request for additional information and the additional information shall be submitted through the EU portal.~~

6. Between the submission date referred to in paragraph 1 and the expiry of

the period referred to in paragraph 3, only the reporting Member State may request additional information from the sponsor concerning the aspects covered in Part I of the assessment report, taking into account the considerations referred to in paragraph 5.

For the purpose of obtaining and reviewing this additional information from the sponsor in accordance with the third and fourth subparagraphs, the reporting Member State may extend the period referred to in the first subparagraph of paragraph 3 by a maximum of 28 days.

The sponsor shall submit the requested additional information within the period set by the reporting Member State, which shall not exceed 14 days from receipt of the request.

Upon receipt of the additional information the reporting Member State, the additional Member State concerned and all other Member States concerned shall review any additional information provided by the sponsor together with the original application and shall share any unaddressed considerations relevant to the application. The coordinated review shall be performed within a maximum of seven days from the receipt of the additional information and the further consolidation shall be performed within a maximum of seven days from the end of the coordinated review. The reporting Member State shall take due account of the considerations of the Member States concerned and shall record how the considerations have been dealt with.

Where the sponsor does not provide additional information within the period set by the reporting Member State in accordance with the third subparagraph, the application shall be deemed to have lapsed in the additional Member State concerned.

The request for additional information and the additional information shall be submitted through the EU portal.

~~7. The additional Member State concerned shall assess, for its territory, the aspects addressed in Part II of the assessment report within the period referred to in paragraph 3 and submit, through the EU portal, Part II of the assessment report, including its conclusion, to the sponsor. Within that period it may request, with justified reasons, additional information from the sponsor regarding aspects addressed in Part II of the assessment report as far as its territory is concerned~~

7. The additional Member State concerned shall assess, for its territory, the aspects covered in Part II of the assessment report and submit Part II assessment report, including its conclusions, through the EU portal, to the sponsor.

Within period referred to in paragraph 3, additional Member State may request, through the EU portal, with justified reasons, additional information from the sponsor regarding aspects covered in Part II of the assessment report as far as its territory is concerned.

~~8. For the purpose of obtaining and reviewing the additional information referred to in paragraph 7 from the sponsor in accordance with the second and third subparagraphs, the additional Member State concerned may extend the period referred to in paragraph 7 by a maximum of 31 days.~~

~~The sponsor shall submit the requested additional information within the period set by the additional Member State concerned which shall not exceed 12 days from receipt of the request.~~

~~Upon receipt of the additional information, the Member State concerned shall complete its assessment within a maximum of 19 days.~~

~~Where the sponsor does not provide additional information within the period set by the additional Member State concerned in accordance with the second subparagraph, the application shall be deemed to have lapsed in the additional Member State concerned.~~

~~The request for additional information and the additional information shall be submitted through the EU portal.~~

8. For the purpose of obtaining and reviewing the additional information referred to in paragraph 6 or 7 the additional Member State concerned may extend the period referred to in paragraph 5 by maximum of 28 days.

The sponsor shall submit the requested additional information within the period set by the additional Member State concerned, which shall not exceed 14 days from the receipt of the request.

Upon receipt of the additional information, the Member State concerned shall complete its assessment within a maximum of 14 days.

Where the sponsor does not provide additional information within the period set by the additional Member State concerned in accordance with second subparagraph, the application shall be deemed to have lapsed in the additional Member State concerned

~~9. Where, regarding the aspects covered by Part I of the assessment report, the conduct of the clinical trial is acceptable or acceptable subject to compliance with specific conditions, the additional Member State concerned shall include in its decision its conclusion on Part II of the assessment report.~~

~~10. The additional Member State concerned shall refuse to authorise the clinical trial if it disagrees with the conclusion of the reporting Member State as regards Part I of the assessment report on any of the grounds referred to in second subparagraph of paragraph 4, or if it finds, on duly justified grounds, that the aspects addressed in Part II of the assessment report are not complied with, or where an ethics committee has issued a negative opinion which, in accordance with the law of the additional Member State concerned, is valid for that entire additional Member State. That additional Member State concerned shall~~

provide for an appeal procedure in respect of such refusal.

~~11. Where the additional Member State concerned has not notified the sponsor of its decision within the period referred to in paragraph 3, or in case that period has been extended in accordance with paragraph 6 or 8 where that additional Member State concerned has not notified the sponsor of its decision within the extended period, the conclusion on Part I of the assessment report shall be deemed to be the decision of that additional Member State concerned on the application for authorisation of the clinical trial.~~

11. Where the additional Member State concerned has not notified the sponsor of its decision within the period referred to in paragraph 3, or in case that period has been extended in accordance with paragraph 6 or 8 and where that additional Member State concerned has not notified the sponsor of its decision within the extended period, the conclusion on Part I of the assessment report shall be deemed to be the decision of that additional Member State concerned on the application for authorisation of the clinical trial.

~~12. A sponsor shall not submit an application dossier in accordance with this Article where a procedure set out in Chapter II is pending as regards that clinical trial.~~

12. A sponsor shall not submit an application dossier in accordance with this Article where a procedure for a substantial modification of Part I of the assessment report, set out in Chapter III, is pending as regards that clinical trial.

Article 14a

Appointment of a new reporting Member State

1. The reporting Member State may initiate the procedure for an appointment of a new reporting Member State if:

(a) the reporting Member State has notified its decision refusing the authorisation of the clinical trial; or

(b) the clinical trial is no longer taking place in the reporting Member State.

2. The procedure can only be launched after the clinical trial has been authorised in at least one Member State concerned.

3. The reporting Member State shall notify the sponsor and other Member States concerned of its intention to cease to be a reporting Member State.

4. The Member States concerned shall declare their willingness to become new reporting Member State. The selection of new reporting Member State shall follow the rules established Article 5a (4) and (5).

5. Following the initiation of the procedure for the appointment of a new reporting Member State, the initial reporting Member State shall continue to carry out its tasks until all of the ongoing assessments and records are completed and the respective final assessment reports are submitted to the EU portal.

6. The new reporting Member State shall become responsible for the assessment of any application related to Part I of the assessment report, including an application based on Article 14, that has been submitted after it has been notified as the reporting Member State to the sponsor and all Member States concerned by the EU portal.

CHAPTER IIa

SPECIAL AUTHORISATION PROCEDURES

Article 14b

Accelerated procedure for the authorisation of multinational clinical trials in the context of public health emergencies

1. During a recognised public health emergency at Union level pursuant to Article 23 of Regulation (EU) 2022/2371 of the European Parliament and of the Council, Member States shall apply an accelerated procedure for the authorisation of multinational clinical trials for medicinal products intended for the treatment, prevention or medical diagnosis of the disease or condition which are directly related to the public health emergency.

2. To address an emergence or development of a serious cross-border threat to health as defined in Article 3(1) of Regulation 2022/2371 that is likely to lead to the recognition of a public health emergency at Union level in accordance with Article 23(1) of Regulation (EU) 2022/2371, Member States shall apply an accelerated procedure for the authorisation of multinational clinical trials when this procedure is declared applicable in accordance with the criteria in paragraph 3 of this Article. The application of the accelerated procedure shall ensure the availability of medicinal products in order to prevent or swiftly contain the emerging serious cross-border health threat, to provide timely treatment options grounded in scientifically robust evidence or to facilitate medical diagnosis of the disease or condition directly related to the specific serious cross-border health threat.

3. The Commission shall, by means of implementing acts, lay down the detailed criteria and the processes for declaring applicability of the accelerated authorisation procedure to address an emergence or development of serious cross-border threat to health that is likely to lead to the recognition of a public health emergency at Union level in accordance with Article 23 (1) of

Regulation (EU) 2022/2371.

The criteria for declaring applicability of an accelerated authorisation procedure shall at least include the epidemiological situation and its dynamics as well as the availability of treatment, prevention and diagnostics options addressing the emerging serious cross-border threat to health. The process of declaring applicability of the accelerated authorisation procedure shall involve consultations with relevant Union agencies, expert groups and advisory bodies in the field of public health and clinical trials.

The implementing acts referred to in the first subparagraph shall be adopted in accordance with the examination procedure referred to in Article 88.

4. When submitting the application for the clinical trial authorisation during a public health emergency as referred to in paragraph 1 or when the accelerated procedure referred to in paragraph 2 is declared applicable to address an emerging serious cross-border health threat, pursuant to the procedure referred to in paragraph 3, the sponsor shall indicate whether the investigational medicinal products are intended for the treatment, prevention or medical diagnosis of a disease or a condition directly related to the specific serious cross-border threat to health. The reporting Member State shall confirm whether the accelerated procedure is applicable to the clinical trial application.

5. The Commission shall adopt delegated acts in accordance with Article 89 to supplement this Regulation by setting out the procedures for an accelerated authorisation of multinational clinical trials, including timelines, criteria for evaluating whether a clinical trial qualifies for an accelerated procedure and an integrated ethical review, and by laying down simplified requirements for the application dossier.

Article 14c
Combined studies

1. This Article applies to combined studies in which a clinical trial is combined with a performance study of an in vitro diagnostic medical device that is subject to authorisation pursuant to Article 58(1) of Regulation (EU) 2017/746, or is combined with a clinical investigation of a medical device that is subject to authorisation according to Article 62 of Regulation (EU) 2017/745.

2. By way of derogation from Article 5, the sponsor of a combined study referred to in paragraph 1, which is to be conducted in one or more Member States, may submit a single application for authorisation.

3. The single application referred to in paragraph 2 shall be submitted electronically through the EU Portal to all Member States in which the combined study is to be conducted ('Member States concerned'). Where a combined study has more than one sponsor, the sponsors shall designate one coordinating sponsor.

4. The Member States concerned shall assess the single application by means of a coordinated assessment procedure under the direction of a reporting Member State chosen from among the Member States concerned. If a combined study involves only one Member State, that Member State shall be the reporting Member State.

5. The coordinated assessment procedure shall include the assessment by the competent authorities and review by ethics committees. During the assessment procedure, the Member States concerned may only raise considerations related to the following:

(a) the grounds referred to in Article 14a(5) of this Regulation, Article 78(8) of Regulation (EU) 2017/746 or Article 74(8) of Regulation (EU) 2017/745; or

(b) issues that would lead to ethics committee of the Member State concerned issuing a negative opinion.

6. Where the conclusion of the reporting Member State as regards the area of coordinated assessment is that the conduct of the combined study is acceptable, or acceptable subject to compliance with specific conditions, that conclusion shall be deemed to be the conclusion of all Member States concerned.

Notwithstanding the first subparagraph of this paragraph, a Member State concerned may disagree with the conclusion of the reporting Member State concerning the area of coordinated assessment but only on one of the following grounds, provided that the corresponding consideration was raised during the assessment process and the Member State concerned has substantiated comments that were not sufficiently addressed:

(a) participation in the combined study would lead to a subject receiving an inferior treatment than in normal clinical practice in the Member State concerned;

(b) infringement of its national law;

(c) with regard to the assessment of the medical device or in vitro medical device, grounds referred to in Article 78(8) of Regulation 2017/746 or Article 74(8) of Regulation (EU) 2017/745, respectively

7. Where a Member State concerned disagrees with the conclusion on the basis of paragraph 5, it shall communicate its disagreement, together with a detailed justification, through the EU Portal, to the Commission, to all other Member States concerned, and to the coordinating sponsor referred to in

paragraph 2.

8. Each Member State concerned shall issue a single decision as to whether the combined study is authorised, whether it is authorised subject to conditions, or whether authorisation is refused and shall notify the coordinating sponsor referred to in paragraph 2.

9. The Commission shall, by means of a delegated act in accordance with Article 89, amend or supplement, as necessary, the provisions of Chapters II to V, VII, XIII, XIV and XVI and Articles 71 and 72 of this Regulation in order to:

(a) enable a streamlined procedure for an authorisation of combined studies, including the coordinated assessment of initial applications, coordinated assessment of the request for substantial modifications and additions of Member State concerned;

(b) set the requirements applicable during the conduct of the combined studies, including as regards to the specific safety reporting requirements;

(a) clarify the responsibilities of the combined studies' sponsors and investigators;

(b) ensure supervision;

(c) determine the functionalities of the EU portal and EU database necessary to support application of this Article.

10. When doing so, the Commission shall take into consideration, where relevant, provisions of Chapter VI and Annex XV of Regulation (EU) 2017/745 or Chapter VI and Annexes XIII and XIV of Regulation (EU) 2017/746 concerning the investigational device(s) or device(s) for performance study which are covered by the combined study, as applicable.

Article 14d

Persons assessing the applications

Article 9 applies to assessments made under this Chapter.

CHAPTER III

AUTHORISATION PROCEDURE FOR A SUBSTANTIAL MODIFICATION OF A CLINICAL TRIAL

Article 15

General principles

A substantial modification, including the addition of a clinical trial site or the change of a principal investigator in the clinical trial site, may only be implemented if it has been approved in accordance with the procedure set out in

this Chapter.

Article 16

Submission of application

~~In order to obtain an authorisation, the sponsor shall submit an application dossier to the Member States concerned through the EU portal.~~

In order to obtain an authorisation, the sponsor shall submit an application dossier to the Member States concerned through the EU portal. The date on which the sponsor submitted the application for an authorisation of a substantial modification is referred to within this Chapter as the submission date.

Article 16a

Parallel substantial modification

1. The sponsor may submit to the reporting Member State, through the EU portal, an application for a parallel substantial modification regarding aspects covered by Part I of the assessment report, prior to the notification of a decision on an ongoing assessment of a substantial modification in accordance with Article 19(1) or Article 23(1).

2. The sponsor may submit to the same Member State concerned, through the EU portal, an application for a parallel substantial modification of an aspect covered by Part II of the assessment report prior to the notification of a decision on an ongoing assessment of a substantial modification in accordance with Article 20(5) or Article 23(1) by the same Member State concerned.

3. The reporting Member State or Member state concerned, as applicable, shall accept the application for a parallel substantial modification if the parallel substantial modification concerns distinct and independent aspects of the application dossier and may be assessed concurrently by the same Member State concerned or reporting Member State.

4. When scope of the application for the parallel substantial modification covers both Part I and Part II of the assessment report, the sponsor shall seek the agreement of both, the reporting Member State and the relevant Member States concerned. The relevant Member State concerned may oppose the agreement if the substantial modification concerns aspects of Part II covered by an ongoing assessment.

Article 17

Validation of an application for the authorisation of a substantial modification of an aspect covered by Part I of the assessment report

- ~~1. The reporting Member State for the authorisation of a substantial modification shall be the reporting Member State for the initial authorisation procedure.~~

~~Member States concerned may communicate to the reporting Member State any considerations relevant to the validation of the application of a substantial modification within five days from the submission of the application dossier.~~

1. The reporting Member State for the authorisation of the substantial modification shall be the reporting Member State for the initial authorisation procedure.

- ~~2. Within six days from the submission of the application dossier, the reporting Member State shall validate the application taking into account considerations expressed by the other Member States concerned and notify the sponsor through the EU portal as to whether:~~

- ~~(a) the substantial modification concerns an aspect covered by Part I of the assessment report; and~~
- ~~(b) the application dossier is complete in accordance with Annex II.~~

2. Within four days from the submission date, the reporting Member State shall validate the application and notify the sponsor through the EU portal as to whether:

- (a) the substantial modification concerns an aspect covered by Part I of the assessment report;**
- (b) the application dossier is complete in accordance with Annex II; and**
- (c) in case of parallel substantial modification to Part I, whether such a parallel substantial modification is acceptable taking into account the requirements of Article 16a.**

When applicable, in the context of a substantial modification of Part I, the Member State concerned shall verify whether the translation or translations in the national language or languages in accordance with the requirements of Articles 26 and 69 has or have been submitted as a substantial modification of Part II. Article 21 applies to the assessment of the accuracy of translations.

3. Where the reporting Member State has not notified the sponsor within the period referred to in paragraph 2, the substantial modification applied for shall be deemed to concern an aspect covered by Part I of the assessment report and the application dossier shall be deemed to be complete.
- ~~4. Where the reporting Member State, taking into account considerations expressed~~

by the other Member States concerned, finds that the application does not concern an aspect covered by Part I of the assessment report or that the application dossier is not complete, it shall inform the sponsor thereof through the EU portal and shall set a maximum of 10 days for the sponsor to comment on the application or to complete the application dossier through the EU portal.

Within five days from receipt of the comments or the completed application dossier, the reporting Member State shall notify the sponsor as to whether or not the application complies with the requirements set out in points (a) and (b) of paragraph 2.

Where the reporting Member State has not notified the sponsor within the period referred to in the second sub-paragraph, the substantial modification applied for shall be deemed to concern an aspect covered by Part I of the assessment report and the application dossier shall be deemed to be complete.

Where the sponsor has not provided comments or completed the application dossier within the period referred to in the first subparagraph, the application shall be deemed to have lapsed in all Member States concerned.

4. Where the reporting Member State finds that the application does not concern an aspect covered by Part I of the assessment report or that the application dossier is not complete or, where applicable, that the parallel substantial modification is not acceptable, it shall inform the sponsor thereof through the EU portal and shall set a maximum of four days for the sponsor to comment on the application or to complete the application dossier through the EU portal.

The reporting Member State shall notify the sponsor within 14 days from the submission date, as to whether or not the application complies with the requirements set out in paragraph 2, points (a), (b), and when applicable point (c).

Where the reporting Member State has not notified the sponsor within the period referred to in the second subparagraph, the substantial modification applied for shall be deemed to concern an aspect covered by Part I of the assessment report, the application dossier shall be deemed to be complete and, when applicable, the parallel substantial modification shall be deemed to be acceptable taking into account the requirements of Article 16a.

Where the sponsor has not provided comments or completed the application dossier within the period referred to in the first subparagraph, the application shall be deemed to have lapsed in all the Member States concerned.

5. For the purposes of Articles 18, 19 and 22, the date on which the sponsor is notified in accordance with paragraph 2 or 4 shall be the validation date of the application. Where the sponsor is not notified, the validation date shall be the last day of the respective periods referred to in paragraphs 2 and 4.

Article 18

Assessment of a substantial modification of an aspect covered by Part I of the assessment report

1. The reporting Member State shall assess the application with regard to an aspect covered by Part I of the assessment report, including whether the clinical trial will remain a low-intervention clinical trial after its substantial modification, and draw up an assessment report.
2. The assessment report shall contain one of the following conclusions concerning the aspects addressed in Part I of the assessment report:
 - (a) the substantial modification is acceptable in view of the requirements set out in this Regulation;
 - (b) the substantial modification is acceptable in view of the requirements set out in this Regulation, but subject to compliance with specific conditions which shall be specifically listed in that conclusion; or
 - (c) the substantial modification is not acceptable in view of the requirements set out in this Regulation.
- ~~3. The reporting Member State shall submit, through the EU portal, the final assessment report including its conclusion, to the sponsor and to the other Member States concerned within 36 days from the validation date.~~

~~For the purposes of this Article and Articles 19 and 23, the reporting date shall be the date on which the final assessment report is submitted to the sponsor and to the other Member States concerned.~~

3. The reporting Member State shall submit, through the EU portal, the final assessment report including its conclusions, to the sponsor and to the other Member States concerned within 28 days from the submission date.

For the purpose of this Article and of Articles 19 and 23, the reporting date shall be the date on which the final assessment report is submitted to the sponsor and the other Member States concerned.

- ~~4. For clinical trials involving more than one Member State the assessment process of substantial modification shall include three phases:
 - (a) an initial assessment phase performed by the reporting Member State within 19 days from the validation date;~~

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- ~~(b) a coordinated review phase performed within 12 days from the end of the initial assessment phase involving all Member States concerned; and~~
- ~~(c) a consolidation phase performed by the reporting Member State within seven days from the end of coordinated review phase.~~

~~During the initial assessment phase, the reporting Member State shall develop a draft assessment report and circulate it to all Member States concerned.~~

~~During the coordinated review phase, all Member States concerned shall jointly review the application based on the draft assessment report and shall share any considerations relevant to the application.~~

~~During the consolidation phase, the reporting Member State shall take due account of the considerations of the other Member States concerned when finalising the assessment report and shall record how all such considerations have been dealt with. The reporting Member State shall submit the final assessment report to the sponsor and all other Member States concerned by the reporting date.~~

4. For clinical trials involving more than one Member State the assessment process of substantial modification shall include three phases:

- (a) an assessment phase performed by the reporting Member State within 21 days from the submission date. The assessment phase shall end when the reporting Member State circulates the draft assessment report;**
- (b) a review phase performed within three days from the end of the assessment phase, involving all the Member States concerned, and;**
- (c) a coordination phase performed within four days from the end of the review phase.**

During the assessment phase, the reporting Member State shall develop a draft assessment report and circulate it to all the Member States concerned.

During the review phase, all Member States concerned shall review the application on the basis of the draft assessment report and shall share considerations for their Member State that are relevant to the application.

Considerations may only be raised on:

- one or more grounds referred to in Article 19(2) of this Regulation.**
- on matters that would lead the ethics committee issuing negative opinion.**

During the consolidation phase, the reporting Member State shall take due account of the considerations of the other Member States concerned when finalizing the assessment report and shall record how the considerations have been addressed. The reporting Member State shall submit the final assessment report to the sponsor and all the other Member States concerned by the reporting date.

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5. ~~The reporting Member State may extend the period referred to in paragraph 3 by a further 50 days for clinical trials involving an advanced therapy investigational medicinal product or a medicinal product as set out in point 1 of the Annex to Regulation (EC) No 726/2004, for the purpose of consulting with experts. In such case, the periods referred to in paragraphs 4 and 6 of this Article shall apply *mutatis mutandis*.~~
6. ~~Between the validation date and the reporting date, only the reporting Member State may request additional information from the sponsor, taking into account the considerations referred to in paragraph 4.~~

~~For the purpose of obtaining and reviewing this additional information from the sponsor in accordance with the third and fourth subparagraph, the reporting Member State may extend the period referred to in the first subparagraph of paragraph 3 by a maximum of 31 days.~~

~~The sponsor shall submit the requested additional information within the period set by the reporting Member State which shall not exceed 12 days from receipt of the request.~~

~~Upon receipt of the additional information, the Member States concerned shall jointly review any additional information provided by the sponsor together with the original application and shall share any considerations relevant to the application. The coordinated review shall be performed within a maximum of 12 days from receipt of the additional information and the further consolidation shall be performed within a maximum of seven days from the end of the coordinated review. When finalising the assessment report, the reporting Member State shall take due account of the considerations of the other Member States concerned and shall record how all such considerations have been dealt with.~~

~~Where the sponsor does not provide additional information within the period determined by the reporting Member State in accordance with the third subparagraph, the application shall be deemed to have lapsed in all Member States concerned.~~

~~The request for additional information and the additional information shall be submitted through the EU portal.~~

6. Between the validation date and the reporting date, only the reporting Member State may request additional information from the sponsor, taking into account the considerations referred to in paragraph 4.

For the purpose of obtaining and reviewing this additional information from the sponsor in accordance with the third and fourth subparagraph, the reporting Member State may extend the period referred to in the first

subparagraph of paragraph 3 by a maximum of 14 days.

The sponsor shall submit the requested additional information within the period set by the reporting Member State. This period shall not extend beyond seven days from the receipt of the request.

Upon receipt of the additional information, the Member States concerned shall review any additional information provided by the sponsor and shall share any unaddressed considerations relevant to the application. The review shall be performed within a maximum of three days from the receipt of the additional information and further consolidation shall be performed within a maximum of seven days from the receipt of additional information from the sponsor. When finalising the assessment report, the reporting Member State shall take due account of the considerations of the other Member States concerned and shall record how the considerations have been dealt with.

Article 19

Decision on the substantial modification of an aspect covered by Part I of the assessment report

- ~~1. Each Member State concerned shall notify the sponsor through the EU portal as to whether the substantial modification is authorised, whether it is authorised subject to conditions, or whether authorisation is refused.~~

~~Notification shall be done by way of a single decision within five days from the reporting date.~~

~~An authorisation of a substantial modification subject to conditions is restricted to conditions which by their nature cannot be fulfilled at the time of that authorisation.~~

1. Each Member State concerned shall notify the sponsor through the EU portal as to whether the substantial modification is authorised, whether it is authorised subject to conditions, or whether authorisation is refused.

Notification shall be done by way of a single decision within five days from the reporting date.

Where the conclusion of the reporting Member State is that the substantial modification is acceptable or acceptable subject to compliance with specific conditions, that conclusions shall be deemed to be the conclusions of the Member State concerned.

A substantial modification subject to condition may be implemented unless the Member State concerned specified that the condition is suspensive. Unless otherwise specified, the fulfilment of the condition does not require a

submission of a request for another substantial modification.

Notwithstanding the first subparagraph, a Member State concerned may disagree with that conclusion of the reporting Member State only on the following grounds, provided that the consideration was raised during the process pursuant to Article 18(4) and it considers that it was not sufficiently addressed:

(a) when it considers that participation in the clinical trial would lead to a subject receiving an inferior treatment than in normal clinical practice in the Member State concerned;

(b) infringement of its national law as referred to in article 90.

- ~~2. Where the conclusion of the reporting Member State is that the substantial modification is acceptable or acceptable subject to compliance with specific conditions, that conclusion shall be deemed to be the conclusion of the Member State concerned.~~

~~Notwithstanding the first subparagraph, a Member State concerned may disagree with that conclusion of the reporting Member State only on the following grounds:~~

~~(a) when it considers that participation in the clinical trial would lead to a subject receiving an inferior treatment than in normal clinical practice in the Member State concerned;~~

~~(b) infringement of its national law as referred to in Article 90;~~

~~(c) considerations as regards subject safety and data reliability and robustness submitted under paragraph 4 or 6 of Article 18.~~

~~Where the Member State concerned disagrees with the conclusion on the basis of the second subparagraph, it shall communicate its disagreement, together with a detailed justification, through the EU portal, to the Commission, to all Member States and to the sponsor.~~

~~A Member State concerned shall refuse to authorise a substantial modification if it disagrees with the conclusion of the reporting Member State as regards Part I of the assessment report on any of the grounds referred to in the second subparagraph, or where an ethics committee has issued a negative opinion which, in accordance with the law of that Member State concerned, is valid for that entire Member State. That Member State shall provide for an appeal procedure in respect of such refusal.~~

2. Where the Member State concerned disagrees with the conclusion on the basis of the second subparagraph, it shall communicate its disagreement, together with a detailed justification, through the EU portal, to the Commission, to all Member States and to the sponsor.

A Member State concerned shall refuse to authorise a substantial modification

if it disagrees with the conclusion of the reporting Member State as regards Part I of the assessment report on any of the grounds referred to in the second paragraph or where an ethics committee has issued a negative opinion which, in accordance with the law of that Member State concerned, is valid for the entire Member State. That Member State shall provide for an appeal procedure in respect of such refusal.

3. Where the conclusion of the reporting Member State, as regards the substantial modification of aspects covered by Part I of the assessment report, is that the substantial modification is not acceptable, that conclusion shall be deemed to be the conclusion of all Member States concerned.
4. Where the Member State concerned has not notified the sponsor of its decision within the period referred to in paragraph 1, the conclusion of the assessment report shall be deemed to be the decision of the Member State concerned on the application for authorisation of the substantial modification.

Article 20

Validation, assessment and decision regarding a substantial modification of an aspect covered by Part II of the assessment report

- ~~1. Within six days from the submission of the application dossier, the Member State concerned shall notify the sponsor through the EU portal of the following:
 - ~~(a) whether the substantial modification concerns an aspect covered by Part II of the assessment report; and~~
 - ~~(b) whether the application dossier is complete in accordance with Annex II.~~~~

1. Within four days from the submission of the application dossier, the Member State concerned shall notify the sponsor through the EU portal of the following:

- (a) whether the substantial modification concerns an aspect covered by Part II of the assessment report;**
 - (b) whether the application dossier is complete in accordance with Annex II;**
 - (c) in case of parallel modification to Part I, whether the submission is acceptable taking into account the requirements of Article 16a.**
- ~~2. Where the Member State concerned has not notified the sponsor within the period referred to in paragraph 1, the substantial modification applied for shall be deemed to concern an aspect covered by Part II of the assessment report and the application dossier shall be deemed to be complete.~~

2. Where the Member State concerned has not notified the sponsor within the period referred to in paragraph 1, the substantial modification applied for shall be deemed to concern an aspect covered by Part II of the assessment report and the application dossier shall be deemed to be complete and, when applicable, the parallel substantial modification shall be deemed to be acceptable taking into account the requirements of Article 16a.

~~3. Where the Member State concerned finds that the substantial modification does not concern an aspect covered by Part II of the assessment report or that the application dossier is not complete, it shall inform the sponsor thereof through the EU portal and shall set a maximum of 10 days for the sponsor to comment on the application or to complete the application dossier through the EU portal.~~

~~Within five days from receipt of the comments or the completed application dossier, the reporting Member State shall notify the sponsor as to whether or not the application complies with the requirements set out in points (a) and (b) of paragraph 1.~~

3. Where the Member State concerned finds that the substantial modification does not concern an aspect covered by Part II of the assessment report or that the application dossier is not complete, or, where applicable, that the parallel substantial modification is not acceptable, it shall inform the sponsor thereof through the EU portal and shall set a maximum of five days for the sponsor to comment on the application or to complete the application dossier through the EU portal.

Within 14 days from the submission date the reporting Member State shall notify the sponsor as to whether or not the application complies with the requirements set out in paragraph 1 points (a), (b), and if applicable, (c).

Where the Member State concerned has not notified the sponsor within the period referred to in the second sub-paragraph, the substantial modification shall be deemed to concern an aspect covered by Part II of the assessment report and the application dossier shall be deemed to be complete.

Where the sponsor has not provided comments nor completed the application dossier within the period referred to in the first subparagraph, the application shall be deemed to have lapsed in the Member State concerned.

4. For the purpose of this Article, the date on which the sponsor is notified in accordance with paragraph 1 or 3 shall be the validation date of the application. Where the sponsor is not notified, the validation date shall be the last day of the respective periods referred to in paragraphs 1 and 3.

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5. The Member State concerned shall assess the application and shall submit to the sponsor, through the EU portal, Part II of the assessment report, including its conclusion, and the decision as to whether the substantial modification is authorised, whether it is authorised subject to conditions, or whether authorisation is refused.

~~Notification shall be done by way of a single decision within 38 days from the validation date.~~

~~An authorisation of a substantial modification subject to conditions is restricted to conditions which by their nature cannot be fulfilled at the time of that authorisation.~~

Notification shall be done by way of a single decision within 28 days from the submission date.

A substantial modification subject to condition may be implemented unless the Member State concerned specified that the condition is suspensive. Unless otherwise specified, a fulfilment of the condition does not require a submission of a request for another substantial modification.

6. During the period referred to in the second subparagraph of paragraph 5, the Member State concerned may request, with justified reasons, additional information from the sponsor regarding the substantial modification as far as its territory is concerned.

~~For the purpose of obtaining and reviewing this additional information from the sponsor, the Member State concerned may extend the period referred to in the second subparagraph of paragraph 5 by a maximum of 31 days.~~

~~The sponsor shall submit the requested additional information within the period set by the Member State concerned which shall not exceed 12 days from receipt of the request.~~

~~Upon receipt of the additional information, the Member State concerned shall complete its assessment within a maximum of 19 days.~~

For the purpose of obtaining and reviewing this additional information from the sponsor, the Member State concerned may extend the period referred to in the paragraph 5, second subparagraph, by a maximum of 14 days.

The sponsor shall submit the requested additional information within the period set by the Member State concerned, which shall not exceed seven days from the receipt of the request.

Upon receipt of the additional information, the Member State concerned shall complete its assessment within a maximum seven days.

Where the sponsor does not provide additional information within the period set by the Member State concerned in accordance with the third subparagraph, the

application shall be deemed to have lapsed in that Member State.

The request for additional information and the additional information shall be submitted through the EU portal.

7. A Member State concerned shall refuse to authorise a substantial modification if it finds, on duly justified grounds, that the aspects covered by Part II of the assessment report are not complied with or where an ethics committee has issued a negative opinion which, in accordance with the law of that Member State concerned, is valid for that entire Member State. That Member State shall provide for an appeal procedure in respect of such refusal.
8. Where the Member State concerned has not notified the sponsor of its decision within the periods set out in paragraphs 5 and 6, the substantial modification shall be deemed to be authorised in that Member State.

Article 21

Substantial modification of aspects covered by Parts I and II of the assessment report

- ~~1. Where a substantial modification relates to aspects covered by Parts I and II of the assessment report, the application for authorisation of that substantial modification shall be validated in accordance with Article 17.~~

- 1. Where a substantial modification relates to aspects covered by Parts I and II of the assessment report, the application for an authorisation of that substantial modification shall be validated in accordance with Articles 17 and 20.**

2. The aspects covered by Part I of the assessment report shall be assessed in accordance with Article 18 and the aspects covered by Part II of the assessment report shall be assessed in accordance with Article 22.

Article 22

Assessment of a substantial modification of aspects covered by Parts I and II of the assessment report — Assessment of the aspects covered by Part II of the assessment report

- ~~1. Each Member State concerned shall assess, for its own territory, the aspects of the substantial modification which are covered by Part II of the assessment report and submit, through the EU portal, that report, including its conclusion, to the sponsor within 38 days from the validation date.~~

- 1. Each Member State concerned shall assess, for its own territory, the aspects**

of the substantial modification which are covered by Part II of the assessment report and submit, through the EU portal, that report, including its conclusion, to the sponsor within 28 days from the submission date. If the reporting Member State requested additional information regarding aspects covered by Part I of the assessment report as per Article 21(2) in conjunction with Article 18(6), or when a Member State concerned requests additional information from the sponsor regarding Part II aspects of the application, Member States concerned may extend this period by 14 days

- ~~2. During the period referred to in paragraph 1, the Member State concerned may request, with justified reasons, additional information from the sponsor regarding this substantial modification as far as its territory is concerned.~~
- ~~3. For the purpose of obtaining and reviewing the additional information referred to in paragraph 2 from the sponsor in accordance with the third and fourth subparagraph, the Member State concerned may extend the period referred to paragraph 1 by a maximum of 31 days.~~

~~The sponsor shall submit the requested additional information within the period set by the Member State concerned which shall not exceed 12 days from the receipt of the request.~~

~~Upon receipt of the additional information, the Member State concerned shall complete its assessment within a maximum of 19 days.~~

~~Where the sponsor does not provide the requested additional information within the period set by the Member State concerned in accordance with the second subparagraph, the application shall be deemed to have lapsed in that Member State.~~

~~The request for additional information and the additional information shall be submitted through the EU portal.~~

3. The sponsor shall submit the requested additional information within the period set by the Member State concerned, which shall not exceed seven days from the receipt of the request.

Upon receipt of the additional information, the Member State concerned shall complete its assessment within a maximum of seven days from the submission of the requested information by the sponsor.

Where the sponsor does not provide the requested additional information within the period set by the Member State concerned the application shall be deemed to have lapsed in that Member State.

The request for additional information and the additional information shall be submitted through the EU portal.

Decision on the substantial modification of aspects covered by Parts I and II of the assessment report

1. Each Member State concerned shall notify the sponsor through the EU portal as to whether the substantial modification is authorised, whether it is authorised subject to conditions, or whether authorisation is refused.

Notification shall be done by way of a single decision within five days from the reporting date or from the last day of the assessment period referred to in Article 22, whichever is later.

~~An authorisation of a substantial modification subject to conditions is restricted to conditions which by their nature cannot be fulfilled at the time of that authorisation.~~

A substantial modification subject to condition may be implemented unless the Member State concerned specified that the condition is suspensive. Unless otherwise specified, a fulfilment of the condition does not require a submission of a request for another substantial modification.

2. Where the conclusion of the reporting Member State is that the substantial modification of aspects covered by Part I of the assessment report is acceptable or acceptable subject to compliance with specific conditions, that conclusion shall be deemed to be the conclusion of the Member State concerned.

~~Notwithstanding the first sub-paragraph, a Member State concerned may disagree with the conclusion of the reporting Member State only on the following grounds:~~

- ~~(a) when it considers that participation in the clinical trial would lead to a subject receiving an inferior treatment than in normal clinical practice in the Member State concerned;~~
- ~~(b) infringement of its national law as referred to in Article 90;~~
- ~~(c) considerations as regards subject safety and data reliability and robustness submitted under paragraph 4 or 6 of Article 18.~~

Notwithstanding the first subparagraph, a Member State concerned may disagree with the conclusion of the reporting Member State only on the following grounds, provided that the consideration was raised during the process pursuant to Article 18(4) and it considers that it was not sufficiently addressed:

- (a) when it considers that participation in the clinical trial would lead to a subject receiving an inferior treatment than in normal clinical practice in the Member State concerned;**
- (b) infringement of its national law as referred to in Article 90.**

Where the Member State concerned disagrees with the conclusion regarding the substantial modification of aspects covered by Part I of the assessment report on the basis of the second subparagraph, it shall communicate its disagreement, together with a detailed justification through the EU portal to the Commission, to all Member States, and to the sponsor.

3. Where, regarding the substantial modification of aspects covered by Part I of the assessment report, the substantial modification is acceptable or acceptable subject to compliance with specific conditions, the Member State concerned shall include in its decision its conclusion on the substantial modification of aspects covered by Part II of the assessment report.
4. A Member State concerned shall refuse to authorise a substantial modification if it disagrees with the conclusion of the reporting Member State as regards the substantial modification of aspects covered by Part I of the assessment report on any of the grounds referred to in second subparagraph of paragraph 2, or if it finds, on duly justified grounds, that the aspects covered by Part II of the assessment report are not complied with, or where an ethics committee has issued a negative opinion which in accordance with the law of the Member State concerned, is valid for that entire Member State. That Member State concerned shall provide for an appeal procedure in respect of such refusal.
5. Where the conclusion of the reporting Member State as regards the substantial modification of aspects covered by Part I of the assessment report is that the substantial modification is not acceptable, that conclusion shall be deemed to be the conclusion of the Member State concerned.
6. Where the Member State concerned has not notified the sponsor of its decision within the periods referred to in paragraph 1, the conclusion on the substantial modification of aspects covered by Part I of the assessment report shall be deemed to be the decision of the Member State concerned on the application for authorisation of the substantial modification.

Article 24

Persons assessing the application for a substantial modification

Article 9 applies to assessments made under this Chapter.

CHAPTER IV

APPLICATION DOSSIER

Article 25

Data submitted in the application dossier

1. The application dossier for the authorisation of a clinical trial shall contain all required documentation and information necessary for the validation and assessment referred to in Chapter II and relating to:

- (a) the conduct of the clinical trial, including the scientific context and arrangements taken,
- (b) the sponsor, investigators, potential subjects, subjects, and clinical trial sites;
- (c) the investigational medicinal products and, where necessary, the auxiliary medicinal products, in particular their properties, labelling, manufacturing and control;
- (d) measures to protect subjects;
- ~~(e) justification as to why the clinical trial is a low-intervention clinical trial, in cases where this is claimed by the sponsor.~~

(e) justification as to why the clinical trial is a minimal-intervention or low-intervention clinical trial, in cases where this is claimed by the sponsor.

The list of required documentation and information is set out in Annex I.

The list of required documentation and information for Part I is set out in Part I of Annex I. The list of required documentation for Part II is set out in Part II of Annex I.

1a. The requirements for Part I may be adapted for minimal-intervention or low-intervention clinical trials.

1b. The sponsor shall use harmonised templates, where such templates are available, for the submission of documents for Part II of the application dossier necessary for the authorisation of the clinical trial, in accordance with the requirements described in Article 7(1) of this Regulation.

1c. To draw up and update, when necessary, harmonised templates to be used by sponsors, the Commission shall be empowered to adopt implementing acts in accordance with Article 88. The harmonised templates may include standardised sections for documents referred to in Article 7(2) and in Annex I.

2. The application dossier for the authorisation of a substantial modification shall contain all required documentation and information necessary for the validation and assessment referred to in Chapter III:

- (a) a reference to the clinical trial or clinical trials which are substantially modified using the EU trial number referred to in the third subparagraph of Article 81(1) (the 'EU trial number');
- (b) a clear description of the substantial modification, in particular, the nature of and

the reasons for substantial modification;

- (c) a presentation of data and additional information in support of the substantial modification, where necessary;
- (d) a clear description of the consequences of the substantial modification as regards the rights and safety of the subject and the reliability and robustness of the data generated in the clinical trial.

The list of required documentation and information is set out in Annex II.

2a. The requirements referred to in paragraph 2 may be adapted for minimal-intervention and low-intervention clinical trials.

- 3. 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, as applicable at the time of performance of those studies.
- 4. Where reference is made in the application dossier to data generated in a clinical trial, that clinical trial shall have been conducted in accordance with this Regulation or, if conducted prior to the date referred to in the second paragraph of Article 99, in accordance with Directive 2001/20/EC.
- 5. Where the clinical trial referred to in paragraph 4 has been conducted outside the Union, it shall have been conducted in accordance with principles equivalent to those of this Regulation as regards the rights and safety of the subject and the reliability and robustness of the data generated in the clinical trial.
- 6. Data from a clinical trial started as from the date referred to in the second paragraph of Article 99 shall 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.

Data from a clinical trial started before the date referred to in the second paragraph of Article 99 shall only be submitted in an application dossier if that clinical trial is registered in a public register which is a primary or partner registry of, or a data provider to, the WHO ICTRP or if the results of that clinical trial have been published in an independent peer-reviewed scientific publication.

- 7. Data submitted in an application dossier which do not comply with paragraphs 3 to 6 shall not be considered in the assessment of an application for authorisation of a clinical trial or of a substantial modification.

8. An application dossier for an authorisation of a clinical trial or for an authorisation of a substantial modification may rely on health data accessed under Chapter IV of Regulation (EU) 2025/327 of the European Parliament and of the Council*

* Regulation (EU) 2025/327 of the European Parliament and of the Council of 11 February 2025 on the European Health Data Space and amending Directive 2011/24/EU and Regulation (EU) 2024/2847 (OJ L, 2025/327, 5.3.2025).

9. National competent authorities and ethics committees shall ensure that the persons validating or assessing the initial application and substantial modification requests only documents which are listed in Part I and Part II of Annex I and Annex II.

Article 26

Language requirements

The language of the application dossier, or parts thereof, shall be determined by the Member State concerned.

Member States, in applying the first paragraph, shall consider accepting, for the documentation not addressed to the subject, a commonly understood language in the medical field.

Article 27

Update by way of delegated acts

The Commission shall be empowered to adopt delegated acts in accordance with Article 85 in respect of amending Annexes I and II in order to adapt them to technical progress or to take account of international regulatory developments in which the Union or the Member States are involved, in the field of clinical trials.

CHAPTER IVa

INVESTIGATIONAL MEDICINAL PRODUCT CORE DOSSIER

Article 27a

Establishment of an investigational medicinal product core dossier

1. At the time of submission of a clinical trial application referred to in Articles 5 and 11 the sponsor may request through the EU portal the establishment of an investigational medicinal product core dossier. To this end, the sponsor shall provide data and information referred to in point (Ga) of Part I of Annex I.

2. The sponsor shall submit the request for the establishment of the investigational medicinal product core dossier to all Member States concerned of the initial trial. The sponsor may extend this request to other Member States than the Member States concerned. The reporting Member State of the initial clinical trial shall become the depositary Member State.

3. The depositary Member State shall verify the completeness and suitability of the core dossier for the purposes of the initial clinical trial. At the latest by the time when the conclusion of the assessment of Part I is due in accordance with Article 6(3) the depositary Member State shall notify the sponsor and the other core dossier competent Member States through the EU portal of the establishment of the investigational medicinal products core dossier where the assessment is positive.

4. The investigational product core dossier shall be relied upon by the reporting Member State and the Member States concerned in the process of authorising the initial clinical trial referred to in paragraph 1.

5. Once established, the investigational medicinal product core dossier shall be referred to in all subsequent applications concerning the clinical trial in the context of which the investigational medicinal products core dossier was established and any other corresponding clinical trial.

Article 27b

Maintenance and changes of the investigational medicinal products core dossier

1. The sponsor shall keep the investigational medicinal product core dossier updated and shall review it at least once per year. When the sponsor identifies a necessity to update the investigational products core dossier, paragraph 2 applies.

2. When new information, relevant to maintain the suitability and completeness of an established investigational product core dossier becomes known to the sponsor, the sponsor shall submit to the depositary Member State, through the EU portal, a request for a change of the investigational medicinal product core dossier.

3. In case of a new application for an authorisation of a new corresponding clinical trial, the reporting Member State of that clinical trial together with the depositary Member State shall assess the suitability of the investigational product core dossier for the purpose of the authorisation of the trial application, that is;

(a) whether the investigational product core dossier is complete as regards the information on the characteristics and knowledge about the investigational medicinal products;

(b) if appropriate, the compliance with the requirements concerning the manufacturing and import of investigational medicinal products set out in

Chapter IX;

(c) whether the investigator's brochure and the IMPD is adequate and complete for the scope of use as proposed by the sponsor in the application in accordance point Ga, Part I of Annex I.

The reporting Member State of the corresponding clinical trial shall communicate the results of its assessment to the depositary Member State.

If the investigational product core dossier does not contain all the information necessary for the authorisation of the clinical trial, the reporting Member State may request the sponsor to change the investigational product core dossier.

The sponsor shall in such situations request a change of the investigational medicinal product core dossier in accordance with paragraph 2.

4. After receiving the request for a change to the core dossier, independently of whether a change is submitted in the context of an assessment of an application related to a corresponding clinical trial or independently, the depositary Member State shall verify whether the core dossier, once changed, will continue to fulfil the requirements listed in paragraph 3 points (a), (b) and (c). The Member State concerned with the core dossier shall not duplicate the assessment of the depositary Member State. The depositary Member State may consult the Member State concerned as appropriate.

5. If a request for a core dossier change is submitted in the context of an ongoing assessment related to a corresponding clinical trial, the timeline for change of the core dossier shall allow for timely approval of the clinical trial.

6. The sponsor shall assess whether a change to the investigational product core dossier makes it necessary to submit a substantial modification in corresponding clinical trials that are ongoing.

Article 27c

Procedural aspects related to the establishment and maintenance of the investigational medicinal products core dossier

The Commission shall set out the detailed rules governing the submission of a request for the establishment of an investigational product core dossier, its assessment and maintenance by means of implementing acts, including the rules for cooperation between the core dossier competent Member States and the change of depositary Member State. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article

CHAPTER IVb

REGULATORY SANDBOXES AND USE OF AI

Article 27d

Regulatory sandbox

1. The Commission may, pursuant to the procedure set out in paragraph 7, establish and operate a regulatory sandbox at Union level that provides a controlled and time-limited framework to enable, under real-world conditions, the testing of innovative approaches in clinical trials to which the full application of certain requirements of this Regulation is not possible or appropriate and which therefore may require adaptations.

2. The regulatory sandbox under this Regulation may encompass approaches to the authorisation and conduct of the clinical trials and where appropriate, maybe be implemented in coordination and synergies with the regulatory sandboxes established pursuant to Regulation (EU) 2024/1689 with full involvement of competent authorities supervising the sandbox under Regulation (EU) 2024/1689 and in accordance with the relevant procedures and rules for participating in these AI regulatory sandboxes.

3. The activities within a regulatory sandbox shall take place pursuant to a specific plan, for eligible clinical trials, which may be conducted under enhanced regulatory oversight of the Member States concerned. The plan shall clearly identify the requirements of this Regulation that are temporarily adapted or derogated from in the sandbox and that may relate to, as necessary, to source data and documentation requirements, recruitment and informed consent procedures, monitoring and reporting requirements, trial design rules, investigational medicines handling rules, safety reporting rules, site requirements. The plan shall also identify the roles and responsibilities of sponsors, investigators, and manufacturers.

4. A regulatory sandbox may be established only if the following conditions are met:

(a) it is not possible to authorise or conduct a clinical trial in full compliance with the requirements of this Regulation due to innovative approaches in the clinical trial or due to the specificity of the investigational medicinal product;

(b) the approaches referred to in point (a) are expected to contribute to at least one of the following objectives:

(i) increasing the robustness of the data generated in the trial;

(ii) considerably decreasing clinical trial length, and increasing the efficiency of the clinical trial;

(iii) enabling new technologies and approaches in the development of medicinal products that have the potential to positively and distinctively contribute to better prevention, diagnosis, and treatment, as well as increase adherence to treatment plans or improve the efficiency of the provision of health care;

(c) the sandbox provides safeguards to ensure the safety, well-being, and fundamental rights of clinical trial participants, data robustness, and maintained integrity of the clinical trials within the sandbox.

5. The regulatory sandbox shall not affect the supervisory or corrective powers of the Member States concerned and shall operate under the direct supervision of the competent authorities in the Member State concerned for activities that take place on its territory.

6. Before setting up a sandbox, the Commission shall request an opinion of the CTAG.

7. The Commission may establish a regulatory sandbox by means of implementing acts, after taking into consideration opinions referred to in paragraph 6. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 88.

8. Member States shall notify the Commission of any risk to health and safety or fundamental rights or integrity and robustness of data identified during the operation of a sandbox. In these cases, the Commission may, by means of implementing acts, suspend or revoke a regulatory sandbox.

9. Without prejudice to Article 114(1) of [Regulation (EU) .../... of the European Parliament and the Council [reference to be added after adoption cf. COM(2023) 193 final], where in the context of a regulatory sandbox under Article 113 of Regulation (EU) .../... of the European Parliament and the Council [reference to be added after adoption cf. COM(2023) 193 final] is considered that new regulatory approaches in clinical trial are necessary for the product development, the Commission may consider to establish a regulatory sandbox under this Regulation to complement the regulatory sandbox established under Regulation (EU) .../... of the European Parliament and the Council [reference to be added after adoption cf. COM(2023) 193 final].

Article 27e
Use of Artificial Intelligence in Clinical Trials

- 1. For those clinical trials where the sponsor plan to use AI models or systems, the sponsor shall evaluate the benefits and risks related to patient safety and data robustness of the use of the AI in the context of a specific clinical trial for a specific purpose taking into account the guidelines laid down in Article 37 of Regulation [...] [Biotech Act].**
- 2. The sponsor shall provide information in the protocol on the specific purpose of the use of AI models or systems and the description of the process in the context of the specific clinical trial.**
- 3. When the investigation of a medicinal product in a clinical trial is combined with a performance study of an AI in vitro diagnostic medical device or a clinical investigation of an AI medical device, the provisions of Article 14 on coordinated assessment for authorising combined studies shall apply.**
- 4. In cooperation with the CTAG and, where appropriate, the Medical Device Coordination Group, the Artificial Intelligence Board, the Agency shall develop guidelines referred to in paragraph 1 of this Article.**

CHAPTER V

PROTECTION OF SUBJECTS AND INFORMED CONSENT

Article 28
General rules

1. A clinical trial may be conducted only where all of the following conditions are met:
 - (a) the anticipated benefits to the subjects or to public health justify the foreseeable risks and inconveniences and compliance with this condition is constantly monitored;
 - (b) the subjects, or where a subject is not able to give informed consent, his or her legally designated representative, have been informed in accordance with Article 29(2) to (6);
 - (c) the subjects, or where a subject is not able to give informed consent, his or her legally designated representative, have given informed consent in accordance with Article 29(1), (7) and (8);
 - (d) the rights of the subjects to physical and mental integrity, to privacy and to the protection of the data concerning them in accordance with Directive 95/46/EC are safeguarded;

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- (e) the clinical trial has been designed to involve as little pain, discomfort, fear and any other foreseeable risk as possible for the subjects and both the risk threshold and the degree of distress are specifically defined in the protocol and constantly monitored;
 - (f) the medical care provided to the subjects is the responsibility of an appropriately qualified medical doctor or, where appropriate, a qualified dental practitioner;
 - (g) the subject or, where the subject is not able to give informed consent, his or her legally designated representative has been provided with the contact details of an entity where further information can be received in case of need;
 - (h) no undue influence, including that of a financial nature, is exerted on subjects to participate in the clinical trial.

~~2. Without prejudice to Directive 95/46/EC, the sponsor may ask the subject or, where the subject is not able to give informed consent, his or her legally designated representative at the time when the subject or the legally designated representative gives his or her informed consent to participate in the clinical trial to consent to the use of his or her data outside the protocol of the clinical trial exclusively for scientific purposes. That consent may be withdrawn at any time by the subject or his or her legally designated representative.~~

~~The scientific research making use of the data outside the protocol of the clinical trial, shall be conducted in accordance with the applicable law on data protection~~

3. Any subject, or, where the subject is not able to give informed consent, his or her legally designated representative, may, without any resulting detriment and without having to provide any justification, withdraw from the clinical trial at any time by revoking his or her informed consent. ~~Without prejudice to Directive 95/46/EC, the withdrawal of the informed consent shall not affect the activities already carried out and the use of data obtained based on informed consent before its withdrawal.~~

Article 29

Informed consent

1. Informed consent shall be written, dated and signed by the person performing the interview referred to in point (c) of paragraph 2, and by the subject or, where the subject is not able to give informed consent, his or her legally designated representative after having been duly informed in accordance with paragraph 2. Where the subject is unable to write, consent may be given and recorded through appropriate alternative means in the presence of at least one impartial witness. In that case, the witness shall sign and date the informed consent document. The subject or, where the subject is not able to give informed consent, his or her legally designated representative shall be provided with a copy of the document (or the record) by which informed consent has been given. The informed consent shall be documented. Adequate time shall be given for the subject or his or her legally designated representative to consider his or her decision to participate in the clinical trial.

The communication in the context of an interview between the investigator

and the subject or the investigator and the subject and its legally designated representative, as applicable, may be done remotely through use of electronic means. The record of the informed consent procedure may have an electronic form and shall be signed relying on electronic identification means complying with Regulation (EU) No 910/2014 of the European Parliament and of the Council* or the equivalent standards.

2. Information given to the subject or, where the subject is not able to give informed consent, his or her legally designated representative for the purposes of obtaining his or her informed consent shall:

- (a) enable the subject or his or her legally designated representative to understand:
 - (i) the nature, objectives, benefits, implications, risks and inconveniences of the clinical trial;
 - (ii) the subject's rights and guarantees regarding his or her protection, in particular his or her right to refuse to participate and the right to withdraw from the clinical trial at any time without any resulting detriment and without having to provide any justification;
 - (iii) the conditions under which the clinical trial is to be conducted, including the expected duration of the subject's participation in the clinical trial; and
 - (iv) the possible treatment alternatives, including the follow-up measures if the participation of the subject in the clinical trial is discontinued;
- (b) be kept comprehensive, concise, clear, relevant, and understandable to a layperson;
- (c) be provided in a prior interview with a member of the investigating team who is appropriately qualified according to the law of the Member State concerned;
- (d) include information about the applicable damage compensation system referred to in Article 76(1); and
- (e) include the EU trial number and information about the availability of the clinical trial results in accordance with paragraph 6.

3. The information referred to in paragraph 2 shall be prepared in writing and be available to the subject or, where the subject is not able to give informed consent, his or her legally designated representative.

4. In the interview referred to in point (c) of paragraph 2, special attention shall be paid to the information needs of specific patient populations and of individual subjects, as well as to the methods used to give the information.

5. In the interview referred to in point (c) of paragraph 2, it shall be verified that the subject has understood the information.

* Regulation (EU) No 910/2014 of the European Parliament and of the Council of 23 July 2014 on electronic identification and trust services for electronic transactions in the internal market and repealing Directive 1999/93/EC, OJ L 257, 28.8.2014. ELI: <http://data.europa.eu/eli/reg/2014/910/oj>.

6. The subject shall be informed that the summary of the results of the clinical trial and a summary presented in terms understandable to a layperson will be made available in the EU database, referred to in Article 81 (the 'EU data- base'), pursuant to Article 37(4), irrespective of the outcome of the clinical trial, and, to the extent possible, when the summaries become available.

7. This Regulation is without prejudice to national law requiring that both the signature of the incapacitated person and the signature of his or her legally designated representative may be required on the informed consent form.

8. This Regulation is without prejudice to national law requiring that, in addition to the informed consent given by the legally designated representative, a minor who is capable of forming an opinion and assessing the information given to him or her, shall also assent in order to participate in a clinical trial.

Article 30

Informed consent in cluster trials

1. Where a clinical trial is to be conducted exclusively in one Member State, that Member State may, without prejudice to Article 35, and by way of derogation from points (b), (c), and (g) of Article 28(1), Article 29(1), point (c) of Article 29(2), Article 29(3), (4) and (5), points (a), (b) and (c) of Article 31(1) and points (a), (b) and (c) of Article 32(1), allow the investigator to obtain informed consent by the simplified means set out in paragraph 2 of this Article, provided that all of the conditions set out in paragraph 5 of this Article are fulfilled.

2. For clinical trials that fulfil the conditions set out in paragraph 3, informed consent shall be deemed to have been obtained if:

(a) the information required under points (a), (b), (d) and (e) of Article 29(2) is given, in accordance with what is laid down in the protocol, prior to the inclusion of the subject in the clinical trial, and this information makes clear, in particular, that the subject can refuse to participate in, or withdraw at any time from, the clinical trial without any resulting detriment; and

(b) the potential subject, after being informed, does not object to participating in the clinical trial.

3. Informed consent may be obtained by the simplified means set out in paragraph 2, if all the following conditions are fulfilled:

(a) the simplified means for obtaining informed consent do not contradict national law in the Member State concerned;

(b) the methodology of the clinical trial requires that groups of subjects rather than

individual subjects are allocated to receive different investigational medicinal products in a clinical trial;

~~(e) the clinical trial is a low-intervention clinical trial and the investigational medicinal products are used in accordance with the terms of the marketing authorisation;~~

(c) the clinical trial is a minimal-intervention clinical trial;

(d) there are no interventions other than the standard treatment of the subjects concerned;

(e) the protocol justifies the reasons for obtaining informed consent with simplified means and describes the scope of information provided to the subjects, as well as the ways of providing information.

4. The investigator shall document all refusals and withdrawals and shall ensure that no data for the clinical trial are collected from subjects that refuse to participate in or have withdrawn from the clinical trial.

Article 31

Clinical trials on incapacitated subjects

1. In the case of incapacitated subjects who have not given, or have not refused to give, informed consent before the onset of their incapacity, a clinical trial may be conducted only where, in addition to the conditions set out in Article 28, all of the following conditions are met:

(a) the informed consent of their legally designated representative has been obtained;

(b) the incapacitated subjects have received the information referred to in Article 29(2) in a way that is adequate in view of their capacity to understand it;

(c) the explicit wish of an incapacitated subject who is capable of forming an opinion and assessing the information referred to in Article 29(2) to refuse participation in, or to withdraw from, the clinical trial at any time, is respected by the investigator;

(d) no incentives or financial inducements are given to the subjects or their legally designated representatives, except for compensation for expenses and loss of earnings directly related to the participation in the clinical trial;

~~(e) the clinical trial is essential with respect to incapacitated subjects and data of comparable validity cannot be obtained in clinical trials on persons able to give informed consent, or by other research methods;~~

(f) the clinical trial relates directly to a medical condition from which the subject suffers;

(g) there are scientific grounds for expecting that participation in the clinical trial will

produce:

- (i) a direct benefit to the incapacitated subject outweighing the risks and burdens involved; or
 - (ii) some benefit for the population represented by the incapacitated subject concerned when the clinical trial relates directly to the life-threatening or debilitating medical condition from which the subject suffers and such trial will pose only minimal risk to, and will impose minimal burden on, the incapacitated subject concerned in comparison with the standard treatment of the incapacitated subject's condition.
2. Point (g)(ii) of paragraph 1 shall be without prejudice to more stringent national rules prohibiting the conduct of those clinical trials on incapacitated subjects, where there are no scientific grounds to expect that participation in the clinical trial will produce a direct benefit to the subject outweighing the risks and burdens involved.
 3. The subject shall as far as possible take part in the informed consent procedure.

Article 32

Clinical trials on minors

1. A clinical trial on minors may be conducted only where, in addition to the conditions set out in Article 28, all of the following conditions are met:
 - (a) the informed consent of the legally designated representative has been obtained;
 - (b) the minors have received the information referred to in Article 29(2) in a way adapted to their age and mental maturity and from investigators or members of the investigating team who are trained or experienced in working with children;
 - (c) the explicit wish of a minor who is capable of forming an opinion and assessing the information referred to in Article 29(2) to refuse participation in, or to withdraw from, the clinical trial at any time, is respected by the investigator;
 - (d) no incentives or financial inducements are given to the subject or his or her legally designated representative except for compensation for expenses and loss of earnings directly related to the participation in the clinical trial;
 - ~~(e) the clinical trial is intended to investigate treatments for a medical condition that only occurs in minors or the clinical trial is essential with respect to minors to validate data obtained in clinical trials on persons able to give informed consent or by other research methods;~~
 - (f) the clinical trial either relates directly to a medical condition from which the minor concerned suffers or is of such a nature that it can only be carried out on minors;
 - (g) there are scientific grounds for expecting that participation in the clinical trial will

produce:

- (i) a direct benefit for the minor concerned outweighing the risks and burdens involved; or
 - (ii) some benefit for the population represented by the minor concerned and such a clinical trial will pose only minimal risk to, and will impose minimal burden on, the minor concerned in comparison with the standard treatment of the minor's condition.
2. The minor shall take part in the informed consent procedure in a way adapted to his or her age and mental maturity.
3. If during a clinical trial the minor reaches the age of legal competence to give informed consent as defined in the law of the Member State concerned, his or her express informed consent shall be obtained before that subject can continue to participate in the clinical trial.

Article 33

Clinical trials on pregnant or breastfeeding women

A clinical trial on pregnant or breastfeeding women may be conducted only where, in addition to the conditions set out in Article 28, the following conditions are met:

- (a) the clinical trial has the potential to produce a direct benefit for the pregnant or breastfeeding woman concerned, or her embryo, foetus or child after birth, outweighing the risks and burdens involved; or
- (b) if such clinical trial has no direct benefit for the pregnant or breastfeeding woman concerned, or her embryo, foetus or child after birth, it can be conducted only if:
 - (i) a clinical trial of comparable effectiveness cannot be carried out on women who are not pregnant or breast-feeding;
 - (ii) the clinical trial contributes to the attainment of results capable of benefitting pregnant or breastfeeding women or other women in relation to reproduction or other embryos, foetuses or children; and
 - (iii) the clinical trial poses a minimal risk to, and imposes a minimal burden on, the pregnant or breastfeeding woman concerned, her embryo, foetus or child after birth;
- (c) where research is undertaken on breastfeeding women, particular care is taken to avoid any adverse impact on the health of the child; and
- (d) no incentives or financial inducements are given to the subject except for compensation for expenses and loss of earnings directly related to the participation in the clinical trial.

Women who become pregnant or begin breastfeeding while participating in a clinical trial shall not be automatically excluded from participation in the

clinical trial.*Article 34***Additional national measures**

Member States may maintain additional measures regarding persons performing mandatory military service, persons deprived of liberty, persons who, due to a judicial decision, cannot take part in clinical trials, or persons in residential care institutions.

*Article 35***Clinical trials in emergency situations**

1. By way of derogation from points (b) and (c) of Article 28(1), from points (a) and (b) of Article 31(1) and from points (a) and (b) of Article 32(1), informed consent to participate in a clinical trial may be obtained, and information on the clinical trial may be given, after the decision to include the subject in the clinical trial, provided that this decision is taken at the time of the first intervention on the subject, in accordance with the protocol for that clinical trial" and that all of the following conditions are fulfilled:

- (a) due to the urgency of the situation, caused by a sudden life-threatening or other sudden serious medical condition, the subject is unable to provide prior informed consent and to receive prior information on the clinical trial;
- (b) there are scientific grounds to expect that participation of the subject in the clinical trial will have the potential to produce a direct clinically relevant benefit for the subject resulting in a measurable health-related improvement alleviating the suffering and/or improving the health of the subject, or in the diagnosis of its condition;
- (c) it is not possible within the therapeutic window to supply all prior information to and obtain prior informed consent from his or her legally designated representative;
- (d) the investigator certifies that he or she is not aware of any objections to participate in the clinical trial previously expressed by the subject;
- (e) the clinical trial relates directly to the subject's medical condition because of which it is not possible within the therapeutic window to obtain prior informed consent from the subject or from his or her legally designated representative and to supply prior information, and the clinical trial is of such a nature that it may be conducted exclusively in emergency situations;
- (f) the clinical trial poses a minimal risk to, and imposes a minimal burden on, the subject in comparison with the standard treatment of the subject's condition.

2. Following an intervention pursuant to paragraph 1, informed consent in accordance with Article 29 shall be sought to continue the participation of the subject in the clinical trial, and information on the clinical trial shall be given, in accordance with the following requirements:

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- (a) regarding incapacitated subjects and minors, the informed consent shall be sought by the investigator from his or her legally designated representative without undue delay and the information referred to in Article 29(2) shall be given as soon as possible to the subject and to his or her legally designated representative;
 - (b) regarding other subjects, the informed consent shall be sought by the investigator without undue delay from the subject or his or her legally designated representative, whichever is sooner and the information referred to in Article 29(2) shall be given as soon as possible to the the subject or his or her legally designated representative, whichever is sooner.

For the purposes of point (b), where informed consent has been obtained from the legally designated representative, informed consent to continue the participation in the clinical trial shall be obtained from the subject as soon as he or she is capable of giving informed consent.

3. If the subject or, where applicable, his or her legally designated representative does not give consent, he or she shall be informed of the right to object to the use of data obtained from the clinical trial.

CHAPTER VI

START, END, TEMPORARY HALT, AND EARLY TERMINATION OF A CLINICAL TRIAL

Article 36

Notification of the start of a clinical trial and of the end of the recruitment of subjects

1. The sponsor shall notify each Member State concerned of the start of a clinical trial in relation to that Member State through the EU portal.

That notification shall be made within 15 days from the start of the clinical trial in relation to that Member State.

2. The sponsor shall notify each Member State concerned of the first visit of the first subject in relation to that Member State through the EU portal.

That notification shall be made within 15 days from the first visit of the first subject in relation to that Member State.

3. The sponsor shall notify each Member State concerned of the end of the recruitment of subjects for a clinical trial in that Member State through the EU portal.

That notification shall be made within 15 days from the end of the recruitment of subjects. In case of re-start of recruitment, paragraph 1 shall apply.

Article 37

End of a clinical trial, temporary halt and early termination of a clinical trial and submission of the results

1. The sponsor shall notify each Member State concerned of the end of a clinical trial in relation to that Member State through the EU portal.

That notification shall be made within 15 days from the end of the clinical trial in relation to that Member State.

2. The sponsor shall notify each Member State concerned of the end of a clinical trial in all Member States concerned through the EU portal.

That notification shall be made within 15 days from the end of the clinical trial in the last Member State concerned.

3. The sponsor shall notify each Member State concerned of the end of a clinical trial in all Member States concerned and in all third countries in which the clinical trial has been conducted through the EU portal.

That notification shall be made within 15 days from the end of the clinical trial in the last of the Member States concerned and third countries in which the clinical trial has been conducted.

4. Irrespective of the outcome of a clinical trial, within one year from the end of a clinical trial in all Member States concerned, the sponsor shall submit to the EU database a summary of the results of the clinical trial. The content of that summary is set out in Annex IV.

It shall be accompanied by a summary written in a manner that is understandable to laypersons. The content of that summary is set out in Annex V.

However, where, for scientific reasons detailed in the protocol, it is not possible to submit a summary of the results within one year, 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.

In addition to the summary of the results, where the clinical trial was intended to be used for obtaining a marketing authorisation for the investigational medicinal product, the applicant for marketing authorisation shall submit to the EU database the clinical study report 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.

For cases where the sponsor decides to share raw data on a voluntary basis, the Commission shall produce guidelines for the formatting and sharing of those data.

5. The sponsor shall notify each Member State concerned of a temporary halt of a clinical trial in all Member States concerned for reasons not affecting the benefit-risk balance through the EU portal.

That notification shall be made within 15 days from the temporary halt of the clinical trial in all Member States concerned and shall include the reasons for such action.

6. When a temporarily halted clinical trial referred to in paragraph 5 is resumed the sponsor shall notify each Member State concerned through the EU portal.

That notification shall be made within 15 days from the restart of the temporarily halted clinical trial in all Member States concerned.

7. If a temporarily halted clinical trial 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 clinical trial. In the case of early termination of the clinical trial, the date of the early termination shall be deemed to be the date of the end of the clinical trial.

In the case of early termination of the clinical trial for reasons not affecting the benefit-risk balance, 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.

8. Without prejudice to paragraph 4, where the clinical trial protocol provides for an intermediate data analysis date prior to the end of the clinical trial, and the respective results of the clinical trial are available, a summary of those results shall be submitted to the EU database within one year of the intermediate data analysis date.

Article 38

Temporary halt or early termination by the sponsor for reasons of subject safety

1. For the purposes of this Regulation, the temporary halt or early termination of a clinical trial for reasons of a change of the benefit-risk balance shall be notified to the Member States concerned through the EU portal.

That notification shall be made without undue delay but not later than in 15 days of

the date of the temporary halt or early termination. It shall include the reasons for such action and specify follow-up measures.

2. The restart of the clinical trial following a temporary halt as referred to in paragraph 1 shall be deemed to be a substantial modification subject to the authorisation procedure laid down in Chapter III.

Article 39

Update of the contents of the summary of results and summary for laypersons

The Commission shall be empowered to adopt delegated acts in accordance with Article 89 in order to amend Annexes IV and V, in order to adapt them to technical progress or to take account of international regulatory developments, in which the Union or the Member States are involved, in the field of clinical trials.

CHAPTER VII

SAFETY REPORTING IN THE CONTEXT OF A CLINICAL TRIAL

Article 40

Electronic database for safety reporting

1. The European Medicines Agency established by Regulation (EC) No 726/2004 (the 'Agency') shall set up and maintain an electronic database for the reporting provided for in Articles 42 and 43. That database shall be a module of the database referred to in Article 24 of Regulation (EC) No 726/2004 (the 'Eudravigilance database').

2. The Agency shall, in collaboration with Member States, develop a standard web-based structured form for the reporting by sponsors to the database referred to in paragraph 1 of suspected unexpected serious adverse reactions.

Article 41

Reporting of adverse events and serious adverse events by the investigator to the sponsor

1. The investigator shall record and document adverse events or laboratory abnormalities identified in the protocol as critical to the safety evaluation and report them to the sponsor in accordance with the reporting requirements and within the periods specified in the protocol.

2. The investigator shall record and document all adverse events, unless the protocol provides differently. The investigator shall report to the sponsor all serious adverse

events occurring to subjects treated by him or her in the clinical trial, unless the protocol provides differently.

The investigator shall report serious adverse events to the sponsor without undue delay but not later than within 24 hours of obtaining knowledge of the events, unless, for certain serious adverse events, the protocol provides that no immediate reporting is required. Where relevant, the investigator shall send a follow-up report to the sponsor to allow the sponsor to assess whether the serious adverse event has an impact on the benefit-risk balance of the clinical trial.

3. The sponsor shall keep detailed records of all adverse events reported to it by the investigator.
4. If the investigator becomes aware of a serious adverse event with a suspected causal relationship to the investigational medicinal product that occurs after the end of the clinical trial in a subject treated by him or her, the investigator shall, without undue delay, report the serious adverse event to the sponsor.
5. **Reporting requirements of adverse events and serious adverse events for minimal-intervention and low-intervention clinical trials shall be simplified by applying a risk-based approach. Any such adaptation should be clearly stated and justified in the protocol by the sponsor.**

Article 42

Reporting of suspected unexpected serious adverse reactions by the sponsor to the Agency

1. The sponsor of a clinical trial performed in at least one Member State shall report electronically and without delay to the database referred to in Article 40(1) all relevant information about the following suspected unexpected serious adverse reactions.:
 - (a) all suspected unexpected serious adverse reactions to investigational medicinal products occurring in that clinical trial, irrespective of whether the suspected unexpected serious adverse reaction has occurred at a clinical trial site in the Union or in a third country;
 - (b) all suspected unexpected serious adverse reactions related to the same active substance, regardless of pharmaceutical form and strength or indication investigated, in investigational medicinal products used in the clinical trial, occurring in a clinical trial performed exclusively in a third country, if that clinical trial is sponsored:
 - (i) by that sponsor, or
 - (ii) by another sponsor who is either part of the same parent company as the sponsor of the clinical trial, or who develops a medicinal product jointly, on the basis of a formal agreement, with the sponsor of the clinical trial. For this purpose, provision of the investigational medicinal product or information to

a future potential marketing authorisation holder on safety matters shall not be considered a joint development; and

- (c) all suspected unexpected serious adverse reactions to investigational medicinal products occurring in any of the subjects of the clinical trial, which are identified by or come to the attention of the sponsor after the end of the clinical trial.
2. The period for the reporting of suspected unexpected serious adverse reactions by the sponsor to the Agency shall take account of the seriousness of the reaction and shall be as follows:
- (a) in the case of fatal or life-threatening suspected unexpected serious adverse reactions, as soon as possible and in any event not later than seven days after the sponsor became aware of the reaction;
 - (b) in the case of non-fatal or non-life-threatening suspected unexpected serious adverse reactions, not later than 15 days after the sponsor became aware of the reaction;
 - (c) in the case of a suspected unexpected serious adverse reaction which was initially considered to be non-fatal or non-life threatening but which turns out to be fatal or life-threatening, as soon as possible and in any event not later than seven days after the sponsor became aware of the reaction being fatal or life-threatening.

Where necessary to ensure timely reporting the sponsor may, in accordance with section 2.4 of Annex III, submit an initial incomplete report followed up by a complete report.

3. Where a sponsor, due to a lack of resources, does not have the possibility to report to the database referred to in Article 40(1) and the sponsor has the agreement of the Member State concerned, it may report to the Member State where the suspected unexpected serious adverse reaction occurred. That Member State shall report the suspected unexpected serious adverse reaction in accordance with paragraph 1 of this Article.

Article 43

Annual reporting by the sponsor to the Agency

1. Regarding investigational medicinal products other than placebo, the sponsor shall submit annually through the database referred to in Article 40(1) to the Agency a report on the safety of each investigational medicinal product used in a clinical trial for which it is the sponsor.
2. In the case of a clinical trial involving the use of more than one investigational medicinal product, the sponsor may, if provided for in the protocol, submit a single safety report on all investigational medicinal products used in that clinical trial.
3. The annual report referred to in paragraph 1 shall only contain aggregate and anonymised data.

4. The obligation referred to in paragraph 1 starts with the first authorisation of a clinical trial in accordance with this Regulation. It ends with the end of the last clinical trial conducted by the sponsor with the investigational medicinal product.

Article 44

Assessment by Member States

1. The Agency shall, by electronic means, forward to the Member States concerned the information reported in accordance with Article 42 and 43.
2. Member States shall cooperate in assessing the information reported in accordance with Articles 42 and 43. The Commission may, by means of implementing acts, set up and modify the rules on such cooperation. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 88(2).
3. The responsible ethics committee shall be involved in the assessment of the information referred to in paragraphs 1 and 2, if it has been provided for in the law of the Member State concerned.

Article 45

Technical aspects

Technical aspects for safety reporting in accordance with Articles 41 to 44 are contained in Annex III. Where necessary in order to improve the level of protection of subjects, the Commission shall be empowered to adopt delegated acts in accordance with Article 89 in order to amend Annex III for any of the following purposes:

- (a) improving the information on the safety of medicinal products;
- (b) adapting technical requirements to technical progress;
- (c) taking account of international regulatory developments in the field of safety requirements in clinical trials, endorsed by bodies in which the Union or the Member States participate.

Article 46

Reporting with regard to auxiliary medicinal products

Safety reporting with regard to auxiliary medicinal products shall be made in accordance with Chapter 3 of Title IX of Directive 2001/83/EC.

CONDUCT OF A CLINICAL TRIAL, SUPERVISION BY THE SPONSOR, TRAINING AND EXPERIENCE, AUXILIARY MEDICAL PRODUCTS

Article 47

Compliance with the protocol and good clinical practice

The sponsor of a clinical trial and the investigator shall ensure that the clinical trial is conducted in accordance with the protocol and with the principles of good clinical practice.

Without prejudice to any other provision of Union law or Commission guidelines, the sponsor and the investigator, when drawing up the protocol and when applying this Regulation and the protocol, shall also take appropriate account of the quality standards and the ICH guidelines on good clinical practice.

The Commission shall make publicly available the detailed ICH guidelines on good clinical practice referred to in the second paragraph.

Article 48

Monitoring

In order to verify that the rights, safety and well-being of subjects are protected, that the reported data are reliable and robust, and that the conduct of the clinical trial is in compliance with the requirements of this Regulation, the sponsor shall adequately monitor the conduct of a clinical trial. The extent and nature of the monitoring shall be determined by the sponsor on the basis of an assessment that takes into consideration all characteristics of the clinical trial, including the following characteristics:

- (a) whether the clinical trial is **a minimal-intervention or** a low-intervention clinical trial;
- (b) the objective and methodology of the clinical trial; and
- (c) the degree of deviation of the intervention from normal clinical practice.

Article 49

Suitability of individuals involved in conducting the clinical trial

The investigator shall be a medical doctor as defined in national law, or a person following a profession which is recognised in the Member State concerned as qualifying for an investigator because of the necessary scientific knowledge and experience in patient care.

Other individuals involved in conducting a clinical trial shall be suitably qualified by education, training and experience to perform their tasks.

Article 50

Suitability of clinical trial sites

The facilities where the clinical trial is to be conducted shall be suitable for the conduct of the clinical trial in compliance with the requirements of this Regulation.

Article 50a

Delivery of investigational and auxiliary medicinal products through a dispensing pharmacy, an authorised person or directly to the subject

When justified in the protocol, the delivery of investigational medicinal products and auxiliary medicinal products to the clinical trials subjects may be ensured at a distance under the supervision of the investigator.

In case of a minimal-intervention and a low-intervention clinical trial, the distribution of the investigational medicinal products can be ensured in a Member State where the clinical trial has been authorised, under the responsibility of the investigator, through the dispensing pharmacies or by persons authorised to supply medicinal products to the subject.

The protocol and investigator's brochure shall describe the arrangements for direct delivery to subjects or through dispensing pharmacies or persons authorised to supply to the patients, including the roles and responsibilities of all parties involved and procedures for secure handling, storage.

The direct delivery to subjects shall comply with the guidelines referred to in paragraph 1 of Article 63a.

Article 51

Traceability, storage, return and destruction of investigational medicinal products

~~1. Investigational medicinal products shall be traceable. They shall be stored, returned and/or destroyed as appropriate and proportionate to ensure the safety of the subject and the reliability and robustness of the data generated in the clinical trial, in particular, taking into account whether the investigational medicinal product is an authorised investigational medicinal product, and whether the clinical trial is a low-intervention clinical trial.~~

1. Investigational medicinal products shall be traceable. They shall be stored, returned and/or destroyed as appropriate and proportionate to ensure the safety of the subject and the reliability and robustness of the data generated in the clinical trial, in particular, taking into account whether the investigational medicinal product is an authorised investigational medicinal product, and whether the clinical trial is a minimal-intervention or low-intervention clinical trial.

The first subparagraph shall also apply to unauthorised auxiliary medicinal products.

2. The relevant information regarding the traceability, storage, return and destruction of medicinal products referred to in paragraph 1 shall be contained in the application dossier.

Article 52

Reporting of serious breaches

1. The sponsor shall notify the Member States concerned about a serious breach of this Regulation or of the version of the protocol applicable at the time of the breach through the EU portal without undue delay but not later than seven days of becoming aware of that breach.

2. For the purposes of this Article, a ‘serious breach’ means a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.

Article 53

Other reporting obligations relevant for subject safety

1. The sponsor shall notify the Member States concerned through the EU portal of all unexpected events which affect the benefit-risk balance of the clinical trial, but are not suspected unexpected serious adverse reactions as referred to in Article 42. That notification shall be made without undue delay but no later than 15 days from the date the sponsor became aware of this event.

2. ~~The sponsor shall submit to the Member States concerned, through the EU portal, all inspection reports of third country authorities concerning the clinical trial.~~ **The sponsor shall submit to the Member States concerned, through the EU portal, inspection reports of third country authorities concerning the clinical trial and relevant to subject safety.** When requested by a Member State concerned, the sponsor shall submit a translation of the report or of its summary in an official language of the Union indicated in the request.

Article 54

Urgent safety measures

1. Where an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects.

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2. The sponsor shall notify the Member States concerned, through the EU portal, of the event and the measures taken.

That notification shall be made without undue delay but no later than seven days from the date the measures have been taken.

3. This Article is without prejudice to Chapters III and VII.

Article 55

Investigator's brochure

1. The sponsor shall provide the investigator with the investigator's brochure.
2. The investigator's brochure shall be updated where new and relevant safety information becomes available, and shall be reviewed by the sponsor at least once per year.

Article 56

Recording, processing, handling and storage of information

1. All clinical trial information shall be recorded, processed, handled, and stored by the sponsor or investigator, as applicable, in such a way that it can be accurately reported, interpreted and verified while the confidentiality of records and the personal data of the subjects remain protected in accordance with the applicable law on personal data protection.
2. Appropriate technical and organisational measures shall be implemented to protect information and personal data processed against unauthorised or unlawful access, disclosure, dissemination, alteration, or destruction or accidental loss, in particular where the processing involves the transmission over a network.

Article 57

Clinical trial master file

~~The sponsor and the investigator shall keep a clinical trial master file. The clinical trial master file shall at all times contain the essential documents relating to that clinical trial which allow verification of the conduct of a clinical trial and the quality of the data generated, taking into account all characteristics of the clinical trial, including in particular whether the clinical trial is a low-intervention clinical trial. It shall be readily available, and directly accessible upon request, to the Member States.~~

The sponsor and the investigator shall keep a clinical trial master file. The

clinical trial master file shall at all times contain the essential documents relating to that clinical trial which allow verification of the conduct of a clinical trial and the quality of the data generated, taking into account all characteristics of the clinical trial, including in particular whether the clinical trial is a minimal-intervention or low-intervention clinical trial.

The clinical trial master file kept by the investigator and that kept by the sponsor may have a different content if this is justified by the different nature of the responsibilities of the investigator and the sponsor.

Article 58

Archiving of the clinical trial master file

Unless other Union law requires archiving for a longer period, the sponsor and the investigator shall archive the content of the clinical trial master file for at least 25 years after the end of the clinical trial. However, the medical files of subjects shall be archived in accordance with national law.

The content of the clinical trial master file shall be archived in a way that ensures that it is readily available and accessible upon request, to the competent authorities.

Any transfer of ownership of the content of the clinical trial master file shall be documented. The new owner shall assume the responsibilities set out in this Article.

The sponsor shall appoint individuals within its organisation to be responsible for archives. Access to archives shall be restricted to those individuals.

The media used to archive the content of the clinical trial master file shall be such that the content remains complete and legible throughout the period referred to in the first paragraph.

Any alteration to the content of the clinical trial master file shall be traceable.

Article 59

Auxiliary medicinal products

1. Only authorised auxiliary medicinal products may be used in a clinical trial.
2. Paragraph 1 shall not apply where no authorised auxiliary medicinal product is available in the Union or where the sponsor cannot reasonably be expected to use an authorised auxiliary medicinal product. A justification to this effect shall be

included in the protocol.

3. Member States shall ensure that unauthorised auxiliary medicinal products may enter their territories for the purpose of their use in a clinical trial in accordance with paragraph 2.

CHAPTER IX

MANUFACTURING AND IMPORT OF INVESTIGATIONAL MEDICINAL PRODUCTS AND AUXILIARY MEDICINAL PRODUCTS

Article 60

Scope of this Chapter

This Chapter shall apply to the manufacture and import of investigational medicinal products and auxiliary medicinal products.

Article 61

Authorisation of manufacturing and import

1. The manufacturing and import of investigational medicinal products in the Union shall be subject to the holding of an authorisation.

2. In order to obtain the authorisation referred to in paragraph 1, the applicant shall meet the following requirements:

(a) it shall have at its disposal, for manufacture or import, suitable and sufficient premises, technical equipment and control facilities complying with the requirements set out in this Regulation;

(b) it shall have permanently and continuously at its disposal the services of at least one qualified person who fulfils the conditions of qualification set out in Article 49(2) and (3) of Directive 2001/83/EC ('qualified person').

3. The applicant shall specify, in the application for authorisation, the types and pharmaceutical forms of the investigational medicinal product manufactured or imported, the manufacturing or import operations, the manufacturing process where relevant, the site where the investigational medicinal products are to be manufactured or the site in the Union to which they are to be imported, and detailed information concerning the qualified person.

4. Articles 42 to 45, and point (e) of Article 46 of Directive 2001/83/EC shall apply *mutatis mutandis* to the authorisation referred to in paragraph 1.

5. Paragraph 1 shall not apply to any of the following processes:

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- (a) re-labelling or re-packaging, where those processes are carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the Member State concerned to carry out such processes, and if the investigational medicinal products are intended to be used exclusively in hospitals, health centres or clinics taking part in the same clinical trial in the same Member State;
- (b) preparation of radiopharmaceuticals used as diagnostic investigational medicinal products where this process is carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the Member State concerned to carry out such process, and if the investigational medicinal products are intended to be used exclusively in hospitals, health centres or clinics taking part in the same clinical trial in the same Member State;
- (c) the preparation of medicinal products referred to in points (1) and (2) of Article 3 of Directive 2001/83/EC for use as investigational medicinal products, where this process is carried out in hospitals, health centres or clinics legally authorised in the Member State concerned to carry out such process and if the investigational medicinal products are intended to be used exclusively in hospitals, health centres or clinics taking part in the same clinical trial in the same Member State.

~~6. Member States shall make the processes set out in paragraph 5 subject to appropriate and proportionate requirements to ensure subject safety and reliability and robustness of the data generated in the clinical trial. They shall subject the processes to regular inspections.~~

6. Member States shall make the processes set out in paragraph 5 subject to appropriate and proportionate requirements to ensure subject safety and reliability and robustness of the data generated in the clinical trial while taking into account the guidelines referred to in paragraph 7. They shall subject the processes to regular inspections.

7. The inspection working groups referred to in Article 142, point (k) of Regulation (EU) .../... of the European Parliament and the Council [reference to be added after adoption cf. COM(2023) 193 final]*, in agreement with the Commission, may draw up guidelines on general principles applicable to the processes set out in paragraph 5, including for auxiliary medicinal products, and revise them as necessary in order to take account of technical and scientific progress.

Article 62

Responsibilities of the qualified person

1. The qualified person shall ensure that each batch of investigational medicinal

* Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006, COM/2023/193final

products manufactured in or imported into the Union complies with the requirements set out in Article 63 and shall certify that those requirements are fulfilled.

2. The certification referred to in paragraph 1 shall be made available by the sponsor at the request of the Member State concerned.

Article 63

Manufacturing and import

1. Investigational medicinal products shall be manufactured by applying manufacturing practice which ensures the quality of such medicinal products in order to safeguard the safety of the subject and the reliability and robustness of clinical data generated in the clinical trial ('good manufacturing practice'). The Commission shall be empowered to adopt delegated acts in accordance with Article 89 in order to specify the principles and guidelines of good manufacturing practice and the detailed arrangements for inspection for ensuring the quality of investigational medicinal products, taking account of subject safety or data reliability and robustness, technical progress and global regulatory developments in which the Union or the Member States are involved.

In addition, the Commission shall also adopt and publish detailed guidelines in line with those principles of good manufacturing practice and revise them when necessary in order to take account of technical and scientific progress.

2. Paragraph 1 shall not apply to the processes referred to in Article 61(5).

3. Investigational medicinal products imported into the Union shall be manufactured by applying quality standards at least equivalent to those laid down pursuant to paragraph 1.

~~4. The Member States shall ensure compliance with the requirements of this Article by means of inspections.~~

4. The Member States shall ensure compliance with the requirements of this Article by means of inspections. Articles 188, with exception of its paragraph 3 and 4, and 189 of Directive (EU) .../... [reference to be added after adoption cf. COM(2023) 192 final]* and article 52 of Regulation (EU) .../... of the European Parliament and the Council [reference to be added after adoption cf. COM(2023) 193 final] apply mutatis mutandis.**

* Proposal for a DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC COM/2023/192final.

** Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006, COM/2023/193final

Article 63a

Distribution

- 1. The distribution of investigational medicinal shall comply with standards that shall ensure their quality and integrity. The Commission shall adopt delegated acts supplementing this Regulation by determining the standards of good distribution practices for investigational and auxiliary medicinal products taking into account the input of the inspection working groups referred to in Article 142, point (k) of Regulation (EU) .../... of the European Parliament and the Council [reference to be added after adoption cf. COM(2023) 193 final], and update them if necessary to take account of scientific and technical progress.**
- 2. Where the competent authority of the Member State considers it necessary, in particular where there are grounds for suspecting non-compliance with the requirements of this Article, it may carry out inspections to verify the compliance.**
- 3. Arrangements for inspections referred to in Article 63(1) apply mutatis mutandis to inspections of good distribution practices for investigational and auxiliary medicinal products.**

Article 64

Modification of authorised investigational medicinal products

Articles 61, 62 and 63 shall apply to authorised investigational medicinal products only as regards any modification of such products not covered by a marketing authorisation.

Article 65

Manufacturing of auxiliary medicinal products

Where the auxiliary medicinal product is not authorised, or where an authorised auxiliary medicinal product is modified while such modification is not covered by a marketing authorisation, it shall be manufactured according to the good manufacturing practice referred to in Article 63(1) or to at least an equivalent standard, in order to ensure appropriate quality.

CHAPTER X

LABELLING

Article 66

Unauthorised investigational and unauthorised auxiliary medicinal products

1. The following information shall appear on the outer packaging and on the immediate packaging of unauthorised investigational medicinal products and unauthorised auxiliary medicinal products:

- (a) information to identify contact persons or persons involved in the clinical trial;
- (b) information to identify the clinical trial;
- (c) information to identify the medicinal product;
- (d) information related to the use of the medicinal product.

2. The information which is to appear on the outer packaging and immediate packaging shall ensure subject safety and reliability and robustness of the data generated in the clinical trial, while taking account of the design of the clinical trial, whether the products are investigational or auxiliary medicinal product, and whether they are products with particular characteristics.

The information which is to appear on the outer packaging and immediate packaging shall be clearly legible.

A list of information which is to appear on the outer packaging and immediate packaging is set out in Annex VI.

Article 67

Authorised investigational and authorised auxiliary medicinal products

1. Authorised investigational medicinal products and authorised auxiliary medicinal products shall be labelled:

- (a) in accordance with Article 66(1); or
- (b) in accordance with Title V of Directive 2001/83/EC.

2. Notwithstanding point (b) of paragraph 1, where the specific circumstances, provided for in the protocol, of a clinical trial so require in order to ensure the safety of the subject or the reliability and robustness of data generated in a clinical trial, additional particulars relating to the identification of the clinical trial and of the contact person shall appear on the outer packaging and the immediate packaging of authorised investigational medicinal products. A list of these additional particulars appearing on the outer packaging and immediate packaging is set out in section C of Annex VI.

Article 68

Radiopharmaceuticals used as investigational medicinal products or as auxiliary medicinal products for a medical diagnosis

Articles 66 and 67 shall not apply to radiopharmaceuticals used as diagnostic investigational medicinal products or as diagnostic auxiliary medicinal products.

The products referred to in the first paragraph shall be labelled appropriately in order to ensure the safety of the subject and the reliability and robustness of data generated in the clinical trial.

Article 69 **Language**

The language of the information on the label shall be determined by the Member State concerned. The medicinal product may be labelled in several languages.

Article 70 **Delegated act**

The Commission shall be empowered to adopt delegated acts in accordance with Article 89 in respect of amending Annex VI in order to ensure subject safety and the reliability and robustness of data generated in a clinical trial or to take account of technical progress.

CHAPTER XI

SPONSOR AND INVESTIGATOR

Article 71 **Sponsor**

A clinical trial may have one or several sponsors.

Any sponsor may delegate, in a written contract, any or all of its tasks to an individual, a company, an institution or an organisation. Such delegation shall be without prejudice to the responsibility of the sponsor, in particular regarding the safety of subjects and the reliability and robustness of the data generated in the clinical trial.

The investigator and the sponsor may be the same person.

Article 72
Co-sponsorship

1. Without prejudice to Article 74, where a clinical trial has more than one sponsor, all sponsors shall have the responsibilities of a sponsor set out in this Regulation, unless the sponsors decide otherwise in a written contract setting out their respective responsibilities. Where the contract does not specify to which sponsor a given responsibility is attributed, that responsibility shall lie with all sponsors.
2. By way of derogation from paragraph 1, the sponsors shall be jointly responsible for establishing:
 - (a) a sponsor responsible for compliance with the obligations of a sponsor in the authorisation procedures set out in Chapters II and III;
 - (b) a sponsor responsible for being a contact point for receiving all questions from subjects, investigators or any Member State concerned regarding the clinical trial and providing answers to them;
 - (c) a sponsor responsible for implementing the measures taken in accordance with Article 77.

Article 73
Principal investigator

A principal investigator shall ensure compliance of a clinical trial at a clinical trial site with the requirements of this Regulation.

The principal investigator shall assign tasks among the members of the team of investigators in a way which is not compromising the safety of subjects and the reliability and robustness of the data generated in the clinical trial at that clinical trial site.

Article 74
Legal representative of the sponsor in the Union

1. Where the sponsor of a clinical trial is not established in the Union, that sponsor shall ensure that a natural or legal person is established in the Union as its legal representative. Such legal representative shall be responsible for ensuring compliance with the sponsor's obligations pursuant to this Regulation, and shall be the addressee for all communications with the sponsor provided for in this Regulation. Any communication to that legal representative shall be deemed to be a communication to the sponsor.

2. Member States may choose not to apply paragraph 1 as regards clinical trials to be conducted solely on their territory, or on their territory and the territory of a third country, provided that they ensure that the sponsor establishes at least a contact person on their territory in respect of that clinical trial who shall be the addressee for all communications with the sponsor provided for in this Regulation.

3. As regards clinical trials to be conducted in more than one Member State, all those Member States may choose not to apply paragraph 1 provided that they ensure that the sponsor establishes at least a contact person in the Union in respect of that clinical trial who shall be the addressee for all communications with the sponsor provided for in this Regulation.

Article 75
Liability

This Chapter shall not affect the civil and criminal liability of the sponsor, investigator, or persons to whom the sponsor has delegated tasks.

CHAPTER XII

DAMAGE COMPENSATION

Article 76
Damage compensation

1. Member States shall ensure that systems for compensation for any damage suffered by a subject resulting from participation in a clinical trial conducted on their territory are in place in the form of insurance, a guarantee, or a similar arrangement that is equivalent as regards its purpose and which is appropriate to the nature and the extent of the risk.

2. The sponsor and the investigator shall make use of the system referred to in paragraph 1 in the form appropriate for the Member State concerned where the clinical trial is conducted.

~~3. Member States shall not require any additional use of the system referred to in paragraph 1 from the sponsor for low-intervention clinical trials, if any possible damage that could be suffered by a subject resulting from the use of the investigational medicinal product in accordance with the protocol of that specific clinical trial on the territory of that Member State is covered by the applicable compensation system already in place.~~

3. Member States shall not require any additional use of the system referred to in paragraph 1 from the sponsor for minimal or low-intervention clinical trials, if any possible damage that could be suffered by a subject resulting from

the use of the investigational medicinal product in accordance with the protocol of that specific clinical trial on the territory of that Member State is covered by the applicable compensation system already in place.

CHAPTER XIII

SUPERVISION BY MEMBER STATES, UNION INSPECTIONS AND CONTROLS

Article 77

Corrective measures to be taken by Member States

1. Where a Member State concerned has justified grounds for considering that the requirements set out in this Regulation are no longer met, it may take the following measures on its territory:
 - (a) revoke the authorisation of a clinical trial;
 - (b) suspend a clinical trial;
 - (c) require the sponsor to modify any aspect of the clinical trial.
2. Before the Member State concerned takes any of the measures referred to in paragraph 1 it shall, except where immediate action is required, ask the sponsor and/or the investigator for their opinion. That opinion shall be delivered within seven days.
3. The Member State concerned shall immediately after taking a measure referred to in paragraph 1 inform all Member States concerned through the EU portal.
4. Each Member State concerned may consult the other Member States concerned before taking any of the measures referred to in paragraph 1.

Article 78

Member State inspections

~~1. Member States shall appoint inspectors to perform inspections in order to supervise compliance with this Regulation. They shall ensure that those inspectors are adequately qualified and trained.~~

1. The national competent authorities shall organize inspections in order to supervise compliance with this Regulation.
Member States shall appoint inspectors to perform the inspections in order to supervise compliance with this Regulation.

The competent authority of the Member State shall have in place a system of supervision that shall include the following measures:

(a) announced, and where appropriate, unannounced on-site inspections;

(b) remote inspections conducted where justified;

(c) compliance control;

(d) the effective follow up of the measures referred to in points (a), (b) and (c).

2. Inspections shall be conducted under the responsibility of the Member State where the inspection takes place.

3. Where a Member State concerned intends to carry out an inspection on its territory or in a third country with regard to one or several clinical trials which are conducted in more than one Member State concerned, it shall notify its intention to the other Member States concerned, the Commission and the Agency, through the EU portal, and shall inform them of its findings after the inspection.

4. Inspections fees, if any, may be waived for non-commercial sponsors.

5. In order to efficiently use the resources available and to avoid duplications, the Agency shall coordinate the co-operation between Member States concerned on inspections conducted in Member States, in third countries, and inspections conducted in the framework of an application for a marketing authorisation under Regulation (EC) No 726/2004.

~~6. Following an inspection the Member State under whose responsibility the inspection has been conducted shall draw up an inspection report. That Member State shall make the inspection report available to the inspected entity and the sponsor of the relevant clinical trial and shall submit the inspection report through the EU portal.~~

6. Following an inspection, the Member State under whose responsibility the inspection has been conducted, shall draw up an inspection report. That Member State shall make the inspection report available to the inspected entity and the sponsor of the relevant clinical trial and shall submit the inspection report through the EU portal within 90 days after conducting the inspection.

7. The Commission shall specify, by means of implementing acts, the detailed arrangements for the inspection procedures including the qualification and training requirements for inspectors. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 88(2).

8. **Upon a request by one or more competent authorities of the Member State, the inspection referred to in paragraph 1 may be carried out jointly by the inspectors from more than one Member State and the inspectors from the Agency.**

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9. Member States may delegate to another Member State or the Agency the conduct of a good clinical practice inspection. The Commission may adopt a delegated act in accordance with Article 89 to supplement this Regulation by laying down the procedures applicable to joint inspections and delegation of inspections.
10. This Article does not apply to the good manufacturing practice inspections and the good distribution practices inspections related to application of this Regulation, in accordance with Articles 63 and 63a respectively.

Article 79

Union controls

1. ~~The Commission may conduct controls in order to verify:~~
- ~~(a) whether Member States correctly supervise compliance with this Regulation;~~
 - ~~(b) whether the regulatory system applicable to clinical trials conducted outside the Union ensures that point 8 of the Introduction and general principles contained in Annex I to Directive 2001/83/EC is complied with;~~
 - ~~(c) whether the regulatory system applicable to clinical trials conducted outside the Union ensures that Article 25(5) of this Regulation is complied with.~~
2. ~~The Union controls referred to in point (a) of paragraph 1 shall be organised in cooperation with the Member States concerned.~~

~~The Commission shall prepare in cooperation with the Member States a programme for the Union controls referred to in points (b) and (c) of paragraph 1.~~

~~The Commission shall report on the findings of each Union control carried out. Those reports shall, if appropriate, contain recommendations. The Commission shall submit those reports through the EU portal.~~

1. The Commission may conduct controls in order to verify:

(a) whether the Member States correctly supervise compliance with this Regulation;

(b) whether regulatory system applicable to clinical trials conducted outside the Union ensures that the clinical trials references in the applications for marketing authorisations in the Union are designed, implemented and reported on what good clinical practice and ethical principle are concerned, on the basis of principles that are equivalent to the ones established in this Regulation;

(c) whether the regulatory system applicable to clinical trials conducted outside the Union ensures that Article 25(5) of this Regulation is complied

with.

1a. In order to perform the Union controls referred to in paragraph (1) point (a), the Commission may verify whether competent authorities and ethics committees have in place adequate and effective mechanisms to ensure compliance with this Regulation as regards in particular the requirements related to:

(a) validation of the clinical trial application as referred to in Articles 5(3), 17(2) and Article 20;

(b) scientific and ethical review as referred to in Article 4, Articles 6(1), 7(1), 8, 9 and 10, assessment of substantial modifications as referred to in Articles 17 to 22, safety assessment referred to in Article 44;

(c) communication and coordination with other Member States as referred to in Articles 5 to 8, Article 14, Article 17 to 19, Article 22 and 23;

(d) manufacturing and import of investigational medicinal products as referred to in Articles 61 and 63(4);

(e) application of corrective measures and penalties as referred to in Article 77 and 94;

(f) conduct inspections as referred to in Articles 78, 63 and 63a.

2. The Commission shall organise the controls referred to in paragraph 1 in cooperation with the national authorities and shall carry them out in a manner that avoids unnecessary administrative burden.

3. When performing the controls referred to in paragraph 1, the Commission shall consult the relevant best practices.

4. The Commission, in carrying out the controls referred to in paragraph 1, may be supported by experts from the competent authorities or ethics committees.

5. Following each control, the Commission shall:

(a) prepare a draft report on the findings and, where appropriate, include recommendations addressing the shortcomings identified;

(b) send a copy of the draft report referred to in point (a) to the clinical trials national authority concerned for its comments;

(c) take the comments referred to in point (b) into account in preparing the final report; and

(d) submit the final report through the EU portal.

Article 79a
Obligations as regards Union controls

Member States shall cooperate with the Commission in respect of the performance of the Union controls referred to in Article 79 (1). In particular, they shall:

(a) ensure that the necessary technical assistance and the relevant documentation, upon justified request, is being provided to the Commission as well as provide any other support that the Commission requests to enable it to perform controls efficiently and effectively, including facilitating access to all premises or any part thereof, to personnel (interviews) and data, including IT systems of the competent authority that is relevant for the execution of their duties.

(b) take appropriate follow-up measures to remedy the shortcomings identified through those Commission controls.

CHAPTER XIV

IT INFRASTRUCTURE

Article 80
EU portal

The Agency shall, in collaboration with the Member States and the Commission, set up and maintain a portal at Union level as a single entry point for the submission of data and information relating to clinical trials in accordance with this Regulation. The EU portal shall be technically advanced and user-friendly so as to avoid unnecessary work.

Data and information submitted through the EU portal shall be stored in the EU database.

Article 81
EU database

1. The Agency shall, in collaboration with the Member States and the Commission, set up and maintain a EU data- base at Union level. The Agency shall be considered to be the controller of the EU database and shall be responsible for avoiding unnecessary duplication between the EU database and the EudraCT and Eudravigilance databases.

The EU database shall contain the data and information submitted in accordance with this Regulation.

The EU database shall identify each clinical trial by a unique EU trial number. The sponsor shall refer to this EU trial number in any subsequent submission relating or referring to that clinical trial.

~~2. The EU database shall be established to enable cooperation between the competent authorities of the Member States concerned to the extent that it is necessary for the application of this Regulation and to search for specific clinical trials. It shall also facilitate the communication between sponsors and Member States concerned and enable sponsors to refer to previous submissions of an application for authorisation of a clinical trial or a substantial modification. It shall also enable citizens of the Union to have access to clinical information about medicinal products. To this end all data held in the EU database shall be in an easily searchable format, all related data shall be grouped together by way of the EU trial number, and hyperlinks shall be provided to link together related data and documents held on the EU database and other databases managed by the Agency.~~

2. The EU database shall be established to enable cooperation between the competent authorities of the Member States concerned to the extent that it is necessary for the application of this Regulation and to search for specific clinical trials. It shall also enable communication between sponsors and Member States concerned and reporting Member State as appropriate for the purpose of swift regulatory procedures. It shall enable sponsors to refer to previous submissions of an application for authorisation of a clinical trial or a substantial modification. It shall also enable citizens of the Union to have access to clinical information about medicinal products. To this end all data held in the EU database shall be in an easily searchable format, all related data shall be grouped together by way of the EU trial number, and hyperlinks shall be provided to link together related data and documents held on the EU database and other databases managed by the Agency.

3. The EU database shall support the recording and submission to the Medicinal Product Dictionary, contained in the Eudragilance database, of all the data on medicinal products without a marketing authorisation in the Union and substances not authorised as part of a medicinal product in the Union, that are necessary for the maintenance of that dictionary. To this effect and also with the purpose of enabling the sponsor to cross-refer to prior applications, an EU medicinal product number shall be issued for every medicinal product without a marketing authorisation and an EU active substances code shall be issued for each new active substance not previously authorised as part of a medicinal product in the Union. This shall be done before or during the application for authorisation of the first clinical trial with that product or active substance submitted in accordance with this Regulation. Those numbers shall be mentioned in all subsequent applications for clinical trials and for substantial modifications.

The data submitted, in accordance with the first subparagraph, describing medicinal products and substances shall comply with Union and international standards for the identification of medicinal products and active substances. When an

investigational medicinal product which already has a marketing authorisation in the Union and/or an active substance which is part of a medicinal product with a marketing authorisation in the Union, is to be used in a clinical trial, the relevant product and active substance numbers shall be referred to in the application for that clinical trial.

4. The EU database shall be publicly accessible unless, for all or part of the data and information contained therein, confidentiality is justified on any of the following grounds:

- (a) protecting personal data in accordance with Regulation (EC) No 45/2001;
- (b) protecting commercially confidential information, in particular through taking into account the status of the marketing authorisation for the medicinal product, unless there is an overriding public interest in disclosure;
- (c) protecting confidential communication between Member States in relation to the preparation of the assessment report;
- (d) ensuring effective supervision of the conduct of a clinical trial by Member States.

5. Without prejudice to paragraph 4, unless there is an overriding public interest in disclosure, data contained in the application dossier shall not be publicly accessible before the decision on the clinical trial has been made.

6. The EU database shall contain personal data only insofar as this is necessary for the purposes of paragraph 2.

7. No personal data of subjects shall be publicly accessible.

8. The user interface of the EU database shall be available in all official languages of the Union.

~~9. The sponsor shall permanently update in the EU database information on any changes to the clinical trials which are not substantial modifications but are relevant for the supervision of the clinical trial by the Member States concerned.~~

9. The sponsor shall permanently update in the EU database information on any changes to the clinical trials which are not substantial modifications but are relevant for the supervision of the clinical trial. The sponsor shall also update the EU portal to satisfy the condition to which an authorisation decision is subject to. An update may trigger a corrective measure from the reporting Member State or the Member State concerned requiring from the sponsor to submit a substantial modification concerning this change. The Member State concerned may issue such corrective measure within 7 days from the date of the update. The sponsor shall submit the substantial modification within period defined in the corrective measure by the Member

State.

10. The Agency, the Commission and Member States shall ensure that the data subject may effectively exercise his or her rights to information, to access, to rectify and to object in accordance with Regulation (EC) No 45/2001 and national data protection legislation implementing Directive 95/46/EC, respectively. They shall ensure that the data subject may effectively exercise the right of access to data relating to him or her, and the right to have inaccurate or incomplete data corrected or erased. Within their respective responsibilities, the Agency, the Commission and Member States shall ensure that inaccurate and unlawfully processed data are deleted, in accordance with the applicable law. Corrections and deletions shall be carried out as soon as possible, but no later than 60 days of a request being made by a data subject.

Article 82

Functionality of the EU portal and the EU database

1. The Agency shall, in collaboration with the Member States and the Commission, draw up the functional specifications for the EU portal and the EU database, together with the time frame for their implementation.
2. The Management Board of the Agency shall, on the basis of an independent audit report, inform the Commission when it has verified that the EU portal and the EU database have achieved full functionality and the systems meet the functional specifications drawn up pursuant to paragraph 1.
3. The Commission shall, when it is satisfied that the conditions referred to in paragraph 2 have been fulfilled, publish a notice to that effect in the *Official Journal of the European Union*.

CHAPTER XV

COOPERATION BETWEEN MEMBER STATES

Article 83

~~National contact points~~

- ~~1. Each Member State shall designate one national contact point in order to facilitate the functioning of the procedures set out in Chapters II and III.~~
- ~~2. Each Member State shall communicate the contact point referred to in paragraph 1 to the Commission. The Commission shall publish a list of the national contact points.~~

Competent authorities and ethics committees

1. Member States shall designate one national contact point to which they confer responsibility for the implementation and practical application of this Regulation. The Commission shall publish a list of national contact points.

2. Each Member State shall communicate the contact point referred to in paragraph 1 to the Commission. Member States shall ensure that competent authorities and ethics committees:

(a) have the necessary powers to perform all the necessary regulatory actions and inspections, pursuant to this Regulation.

(b) have, or have access to, a sufficient number of suitably qualified and experienced personnel, human and financial resources, operational capacity, and expertise, including technical expertise, for the effective and efficient performance of their tasks they have been made responsible for pursuant to this Regulation

Article 83a

Communication and coordination between competent authorities and between ethics committees

1. Where more than one competent authority and ethics committee are responsible for performing regulatory activities or inspections in a Member State for the purpose of applying this Regulation, Member States shall ensure efficient and effective coordination among all the competent authorities and ethics committees concerned in order to guarantee the consistency and effectiveness of the regulatory activities or inspections performed on their territory.

2. Within those Member States, the competent authorities shall cooperate with each other. They shall communicate information to each other for the effective implementation of the regulatory activities and inspections provided for in this Regulation.

Article 84

Support by the Agency and the Commission

The Agency shall support the functioning of the cooperation of the Member States in the framework of the authorisation procedures set out in Chapters II and III of this Regulation by maintaining and updating the EU portal and the EU database in accordance with the experience acquired during the implementation of this Regulation.

The Commission shall support the functioning of the cooperation of the Member States referred to in Article 44(2).

Clinical Trials Coordination and Advisory Group

- ~~1. A Clinical Trials Coordination and Advisory Group (CTAG), composed of the national contact points referred to in Article 83 is hereby established.~~
- ~~2. The CTAG shall have the following tasks:
 - ~~(a) to support the exchange of information between the Member States and the Commission on the experience acquired with regard to the implementation of this Regulation;~~
 - ~~(b) to assist the Commission in providing the support referred to in the second paragraph of Article 84;~~
 - ~~(c) to prepare recommendations on criteria regarding the selection of a reporting Member State.~~~~
- ~~3. The CTAG shall be chaired by a representative of the Commission.~~
- ~~4. The CTAG shall meet at regular intervals and whenever the situation requires, on a request from the Commission or a Member State. Any item of the agenda of the meeting shall be placed at the request of the Commission or a Member State.~~
- ~~5. The secretariat shall be provided by the Commission.~~
- ~~6. The CTAG shall draw up its rules of procedure. The rules of procedure shall be made public.~~

1. A Clinical Trials Coordination and Advisory Group (CTAG) is hereby established.

2. Each Member State shall appoint to the CTAG, for a three-year term which may be renewed once, one member and one alternate each with expertise in the field of clinical trials. The members of the CTAG shall be chosen for their competence and experience in the field of clinical trials. They shall represent the competent national authorities and the ethics committees of the Member States. The names and affiliations of members and alternates shall be made public by the Commission. The alternates shall represent and vote for the members in their absence.

3. For the purpose of the fulfilment of their tasks, CTAG members shall be able to rely on the contribution of experts from national competent authorities and ethics committees. These experts shall participate in CTAG meetings where relevant.

4. The CTAG shall use its best endeavors to reach consensus. If such consensus cannot be reached, the CTAG shall decide by a majority of its

members. Members with diverging positions may request that their position and the grounds on which they are based are recorded.

5. The CTAG shall in particular have the following tasks:

(a) to support the exchange of information between the Member States and the Commission on the experience acquired with regard to the implementation of this Regulation;

(b) to assist the Commission in providing the support referred to in the second paragraph of Article 84;

(c) to prepare recommendations on criteria regarding the selection of a reporting Member State;

(d) to provide strategic steering on a common approach for the application of this Regulation and on the support of the clinical trials ecosystem in the Union;

(e) to contribute to the development of guidance aiming to ensure effective and harmonised implementation of this Regulation.

(f) to contribute to the development of guidelines on the use of the artificial intelligence models and systems in clinical trials in accordance with Article [xx] Regulation (EU) .../... [European Biotech Act]*;

(g) to provide advice, either of its own initiative or at the request of the Commission, in the assessment of any issue related to the implementation of this Regulation;

(h) to contribute to harmonised administrative practice with regard to clinical trials in the Member States;

(i) to provide a recommendation before setting up a regulatory sandbox.

6. The CTAG shall be chaired by a representative of the Commission. The chair shall not take part in votes of the CTAG.

7. The CTAG may issue recommendations and opinions on matters related to clinical trials and shall endorse any guidance related to the application of this Regulation. The Commission shall publish the guidelines endorsed by the CTAG.

8. The CTAG shall meet at regular intervals and whenever the situation requires, on a request from the Commission or a Member State. Any item of the agenda of the meeting shall be placed at the request of the Commission or a Member State.

9. The secretariat shall be provided by the Commission.

10. The CTAG shall draw up its rules of procedure. The rules of procedure shall be made public.

CHAPTER XVI

FEES

Article 86

General principle

This Regulation shall be without prejudice to the possibility for Member States to levy a fee for the activities set out in this Regulation, provided that the level of the fee is set in a transparent manner and on the basis of cost recovery principles. Member States may establish reduced fees for non-commercial clinical trials.

Article 87

One payment per activity per Member State

A Member State shall not require, for an assessment as referred to in Chapters II and III, multiple payments to different bodies involved in this assessment.

CHAPTER XVII

IMPLEMENTING ACTS AND DELEGATED ACTS

Article 88

Committee procedure

1. The Commission shall be assisted by the Standing Committee on Medicinal Products for Human Use established by Directive 2001/83/EC. That committee shall be a committee within the meaning of Regulation (EU) No 182/2011.
2. Where reference is made to this paragraph, Article 5 of Regulation (EU) No 182/2011 shall apply.

Where the committee delivers no opinion, the Commission shall not adopt the draft implementing act and the third subparagraph of Article 5(4) of Regulation (EU) No 182/2011 shall apply.

Article 89

Exercise of the delegation

1. The power to adopt delegated acts is conferred on the Commission subject to the conditions laid down in this Article.

2. The power to adopt delegated acts referred to in Articles 27, 39, 45, 63(1) and 70 shall be conferred on the Commission for a period of five years from the date referred to in the second paragraph of Article 99. The Commission shall draw up a report in respect of the delegated powers not later than six months before the end of the five year period. The delegation of powers shall be tacitly extended for periods of an identical duration, unless the European Parliament or the Council opposes such extension not later than three months before the end of each period.
3. The delegation of power referred to in Articles 27, 39, 45, 63(1) and 70 may be revoked at any time by the European Parliament or by the Council. A decision of revocation shall put an end to the delegation of the power specified in that decision. It shall take effect the day following the publication of the decision in the *Official Journal of the European Union* or at a later date specified therein. It shall not affect the validity of any delegated acts already in force.
4. As soon as it adopts a delegated act, the Commission shall notify it simultaneously to the European Parliament and to the Council.
5. A delegated act adopted pursuant to Articles 27, 39, 45, 63(1) and 70 shall enter into force only if no objection has been expressed either by the European Parliament or the Council within a period of two months from notification of that act to the European Parliament and the Council or if, before the expiry of that period, the European Parliament and the Council have both informed the Commission that they will not object. That period shall be extended by two months at the initiative of the European Parliament or the Council.

CHAPTER XVIII

MISCELLANEOUS PROVISIONS

Article 90

Specific requirements for special groups of medicinal products

This Regulation shall not affect the application of national law prohibiting or restricting the use of any specific type of human or animal cells, or the sale, supply or use of medicinal products containing, consisting of or derived from those cells, or of medicinal products used as abortifacients or of medicinal products containing narcotic substances within the meaning of the relevant international conventions in force such as the Single Convention on Narcotic

Drugs of 1961 of the United Nations. The Member States shall communicate that national law to the Commission.

No gene therapy clinical trials may be carried out which result in modifications to the subject's germ line genetic identity.

Article 91

Relation with other Union legislation

This Regulation shall be without prejudice to Council Directive 97/43/Euratom⁽¹⁾, Council Directive 96/29/Euratom⁽²⁾, Directive 2001/18/EC of the European Parliament and of the Council⁽³⁾, Directive 2004/23/EC of the European Parliament and of the Council⁽⁴⁾, Directive 2002/98/EC of the European Parliament and of the Council⁽⁵⁾, Directive 2010/53/EC of the European Parliament and of the Council⁽⁶⁾, and Directive 2009/41/EC of the European Parliament and of the Council.⁽⁷⁾

Article 92

Investigational medicinal products, other products and procedures, free of charge for the subject

Without prejudice to the Member States' competence for the definition of their

(1) Council Directive 97/43/Euratom of 30 June 1997 on health protection of individuals against the dangers of ionizing radiation in relation to medical exposure, and repealing Directive 84/466/Euratom (OJ L 180, 9.7.1997, p. 22).

(2) Council Directive 96/29/Euratom of 13 May 1996 laying down basic safety standards for the protection of the health of workers and the general public against the dangers arising from ionizing radiation (OJ L 159, 29.6.1996, p. 1).

(3) Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC (OJ L 106, 17.4.2001, p. 1).

(4) Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells (OJ L 102, 7.4.2004, p. 48).

(5) Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC (OJ L 33, 8.2.2003, p. 30).

(6) Directive 2010/53/EU of the European Parliament and of the Council of 7 July 2010 on standards of quality and safety of human organs intended for transplantation (OJ L 207, 6.8.2010, p. 14).

(7) Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms (OJ L 125, 21.5.2009, p. 75).

health policy and for the organisation and delivery of health services and medical care, the costs for investigational medicinal products, auxiliary medicinal products, medical devices used for their administration and procedures specifically required by the protocol shall not be borne by the subject, unless the law of the Member State concerned provides otherwise.

Article 93

Data protection

~~1. Member States shall apply Directive 95/46/EC to the processing of personal data carried out in the Member States pursuant to this Regulation.~~

~~2. Regulation (EC) No 45/2001 shall apply to the processing of personal data carried out by the Commission and the Agency pursuant to this Regulation.~~

1. When carrying out their tasks pursuant to this Regulation sponsors are required to process personal data, including genetic data or data concerning health for the following purposes:

(a) for the submission of applications in accordance with Articles 5, 11, 14 and 16;

(b) to perform research activities in the context of a clinical trial in accordance with the protocol as authorised by the national competent authorities in accordance with point D, Part I of Annex I;

(c) to perform safety operations and reporting in accordance with Articles 41 to 43 and 52 to 54;

(d) to record, process, handle and store information in accordance with Article 56;

(e) to perform archiving in accordance with Article 58;

(f) to submit to the EU portal the summary of the results of the clinical trial, the lay summary, the clinical study report and, where applicable, raw data, in accordance with Article 37(4).

2. When carrying out their tasks pursuant to this Regulation, investigators are required to process personal data, including genetic data or data concerning health for the following purposes:

(a) to perform research activities in the context of a clinical trial in accordance with the protocol as authorised by the national competent authorities in accordance with point D, Part I, Annex I;

(b) to perform safety reporting in accordance with Articles 41 and 54;

(c) to record, process, handle and store information in accordance with Article 56;

(d) to perform archiving in accordance with Article 58.

3. Sponsors and investigators shall make available personal data, including genetic data or data concerning health:

(a) to the competent authorities of the Member States for the purposes of oversight activities, including inspections, in accordance with Article 78;

(b) to the Commission for the purposes of controls, in accordance with Article 79.

4. For the processing assessment leading to the authorisation of clinical trial applications and operations referred to in this Article, sponsors and investigators are controllers within the meaning of Article 4(7) of Regulation (EU) 2016/679.

5. Personal data, including genetic data or data concerning health, shall be retained as long as required pursuant to Article 58 and in accordance with the conditions laid down therein.

6. Personal data collected and processed in accordance with this Regulation may be further processed by the same controller for the purposes of other clinical trials conducted under this Regulation, or for scientific research with the aim of protecting public health, improving standard of care and fostering the innovation capacity of European medical research.

7. By derogation from Article 9(4) of Regulation (EU) 2016/679, Member States may not maintain or introduce further conditions, including limitations, with regard to the processing of personal data, including genetic data or data concerning health in the context of clinical trials carried out in accordance with this Regulation.

8. Processing of personal data referred to in this Article shall be subject to appropriate technical and organisational measures to ensure the protection of the rights and freedoms of data subject. In particular, the controller shall obtain informed consent of the subject in accordance with Article 29 of this Regulation. The controllers shall also apply confidentiality rules concerning access to records and personal data of subjects and apply further safeguards that are appropriate for a specific clinical trial as requested in point D, Part I of Annex I (ak), (al), (am).

Article 94

Penalties

1. Member States shall lay down rules on penalties applicable to infringements of this Regulation and shall take all measures necessary to ensure that they are implemented. The penalties provided for shall be effective, proportionate and dissuasive.
2. The rules referred to in paragraph 1 shall address, inter alia, the following:
 - (a) non-compliance with the provisions laid down in this Regulation on submission of information intended to be made publicly available to the EU database;
 - (b) non-compliance with the provisions laid down in this Regulation on subject

safety.

Article 95

Civil and criminal liability

This Regulation is without prejudice to national and Union law on the civil and criminal liability of a sponsor or an investigator.

CHAPTER XIX

FINAL PROVISIONS

Article 96

Repeal

1. Directive 2001/20/EC is repealed as from the date referred to in the second paragraph of Article 99.
2. References to Directive 2001/20/EC shall be construed as references to this Regulation and shall be read in accordance with the correlation table laid down in Annex VII.

Article 97

Review

~~Five years after the date referred to in the second paragraph of Article 99, and every five years thereafter, the Commission shall present a report to the European Parliament and to the Council on the application of this Regulation. That report shall include an assessment of the impact that the Regulation has had on scientific and technological progress, comprehensive information on the different types of clinical trials authorised pursuant to this Regulation, and the measures required in order to maintain the competitiveness of European clinical research. The Commission shall, if appropriate, present a legislative proposal based on that report in order to update the provisions set out in this Regulation.~~

Five years after the date referred to in Article 99, second subparagraph, and every ten years thereafter, the Commission shall present a report to the European Parliament and to the Council on the application of this Regulation. That report shall include an assessment of the impact that the Regulation has had on scientific and technological progress, comprehensive information on the different types of clinical trials authorised pursuant to

this Regulation, and the measures required in order to maintain the competitiveness of European clinical research. The report shall also assess progress made by monitoring as a key performance indicator the number of addition multinational clinical trials authorised in the Union over the 5-year period of the reporting, compared to the average number of such clinical trials authorised per year in the Union as of 2025;

The Commission shall, if appropriate, present a legislative proposal based on that report in order to update the provisions set out in this Regulation.

Article 98

Transitional provision

1. By way of derogation from Article 96(1) of this Regulation, where the request for authorisation of a clinical trial has been submitted before the date referred to in the second paragraph of Article 99 of this Regulation pursuant to Directive 2001/20/EC, that clinical trial shall continue to be governed by that Directive until three years from that date.
2. By way of derogation from Article 96(1) of this Regulation, where the request for authorisation of a clinical trial is submitted between six months after the date of publication of the notice referred to in Article 82(3) of this Regulation and 18 months after the date of publication of that notice, or, if the publication of that notice occurs earlier than 28 November 2015, where that request is submitted between 28 May 2016 and 28 May 2017, that clinical trial may be started in accordance with Articles 6, 7 and 9 of Directive 2001/20/EC. That clinical trial shall continue to be governed by that Directive until 42 months after the date of publication of the notice referred to in Article 82(3) of this Regulation, or, if that publication occurs earlier than 28 November 2015, until 28 May 2019.

Article 98a

Development plan for the EU Portal and database

The Agency shall be responsible for reporting, on the development, maintenance and, where relevant, adjustment of the EU portal in terms of timing, budgetary compliance and quality.

This would include a submission, after consulting the Commission, of a revised development plan for EU Portal and database to the Agency's Management Board 1 month after entry into force of Regulation (EU).../... of the European Parliament and of the Council [include reference to

Biotech Act proposal].* The development plan shall ensure that all required system functionalities are available by the date of application as defined in Article [..] of Regulation (EU).../...[Biotech Act proposal].

The summary of the development plan with key milestones and timelines [once approved by the Management Board of the Agency] shall be made publicly available at the website of the Agency.

Article 99
Entry into force

This Regulation shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.

It shall apply as from six months after the publication of the notice referred to in Article 82(3), but in any event no earlier than 28 May 2016.

Working Document