►B 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

(Text with EEA relevance)

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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

(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;

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(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

(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;

([1]) Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L 324, 10.12.2007, p. 121).

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(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;

(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;

(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

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minors and of incapacitated subjects, an authorisation or agreement from their legally designated representative to include them in the clinical trial;

(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);

(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;

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(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;

(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.

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

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.

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.

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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.

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4. Where the reporting Member State has not notified the sponsor within the period referred to in the first subparagraph 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.

Article 6

Assessment report — Aspects covered by Part I

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

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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;

— 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

([1]) Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L 378, 27.11.2006, p. 1).

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(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.

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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.

Article 7

Assessment report — Aspects covered by Part II

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.

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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.

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.

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.

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.

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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.

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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 psychosocial 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.

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.

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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.

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.

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.

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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. 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.

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.

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.

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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.

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.

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

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.

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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.

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.

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 subparagraph, 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.

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.

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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 38 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.

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;

(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.

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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.

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.

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:

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(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.

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.

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.

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.

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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.

Where the Member State concerned has not notified the sponsor within the period referred to in the second subparagraph, 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.

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.

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.

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.

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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.

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.

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.

Article 23

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.

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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.

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 subparagraph, 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 suject safety and data reliability and robustness submitted under paragraph 4 or 6 of Article 18.

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. ►C1 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. ◄

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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.

The list of required documentation and information is set out 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.

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

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.

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.

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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;

(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.

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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.

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

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(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.

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 database'), 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 3 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.

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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;

(c) 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;

(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:

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(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 their 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:

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(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 breastfeeding;

(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.

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.

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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:

(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.

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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.

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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.

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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’).

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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.

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:

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(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.

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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 42and 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.

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CHAPTER VIII

CONDUCT OF A CLINICAL TRIAL, SUPERVISION BY THE SPONSOR, TRAINING AND EXPERIENCE, AUXILIARY MEDICINAL 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 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.

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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 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.

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. 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.

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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.

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 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.

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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.

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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:

(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.

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Article 62

Responsibilities of the qualified person

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

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) orto at least an equivalent standard, in order to ensure appropriate quality.

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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.

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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;

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(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.

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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.

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.

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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.

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 cooperation 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.

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).

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.

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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.

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 database 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.

3. The EU database shall support the recording and submission to the Medicinal Product Dictionary, contained in the Eudravigilance 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

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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.

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

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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.

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).

Article 85

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.

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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.

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.

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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.

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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 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]) 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).

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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.

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

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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 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.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

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ANNEX I

APPLICATION DOSSIER FOR THE INITIAL APPLICATION

A. INTRODUCTION AND GENERAL PRINCIPLES

1. The sponsor shall, where appropriate, refer to any previous applications. If these applications have been submitted by another sponsor, the written agreement from that sponsor shall be submitted.

2. Where a clinical trial has more than one sponsor, detailed information of the responsibilities of each of the sponsors shall be submitted in the application dossier.

3. The application shall be signed by the sponsor or a representative of the sponsor. This signature confirms that the sponsor is satisfied that:

   (a) the information provided is complete;

   (b) the attached documents contain an accurate account of the information available;

   (c) the clinical trial is to be conducted in accordance with the protocol; and

   (d) the clinical trial is to be conducted in accordance with this Regulation.

4. The application dossier for an application limited to Part I of the assessment report referred to in Article 11 shall be limited to sections B to J and Q of this Annex.

5. Without prejudice to Article 26, the application dossier for an application limited to Part II of the assessment report referred to in Article 11 and the application dossier for an application referred to in Article 14 shall be limited to sections K to R of this Annex.

B. COVER LETTER

6. The cover letter shall specify the EU trial number and the universal trial number and shall draw attention to any features which are particular to the clinical trial.

7. However, in the cover letter it is not necessary to reproduce information already contained in the EU application form, with the following exceptions:

   (a) specific features of the clinical trial population, such as subjects not able to give informed consent, minors and pregnant or breast-feeding women;

   (b) whether the clinical trial involves the first administration of a new active substance to humans;

   (c) whether scientific advice relating to the clinical trial or the investigational medicinal product has been given by the Agency, a Member State or a third country;

   (d) whether the clinical trial is part or is intended to be part of a Paediatric Investigation Plan (PIP) as referred to in Title II, Chapter 3, of Regulation (EC) No 1901/2006 (if the Agency has already issued a decision on the PIP, the cover letter contains the link to the decision of the Agency on its website);

   (e) whether investigational medicinal products or auxiliary medicinal products are a narcotic, psychotropic or radiopharmaceutical;

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(f) whether the investigational medicinal products consist of or contain a genetically-modified organism or organisms;

(g) whether the sponsor has obtained an orphan designation for the investigational medicinal product for an orphan condition;

(h) a comprehensive list, including the regulatory status, of all investigational medicinal products and a list of all auxiliary medicinal products; and

(i) a list of medical devices which are to be investigated in the clinical trial but which are not part of the investigational medicinal product or products, together with a statement as to whether the medical devices are CE-marked for the intended use.

8. The cover letter shall indicate where the information listed in paragraph 7 is contained in the application dossier.

9. The cover letter shall indicate if the clinical trial is considered by the sponsor to be a low-intervention clinical trial and shall contain a detailed justification thereof.

10. The cover letter shall indicate if 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, and as a consequence whether informed consent will be obtained by simplified means.

11. The cover letter shall indicate the location in the application dossier of the information necessary for assessing whether an adverse reaction is a suspected unexpected serious adverse reaction, that is the reference safety information.

12. In the case of a resubmission, the cover letter shall specify the EU trial number for the previous clinical trial application, highlight the changes as compared to the previous submission and, if applicable, specify how any unresolved issues in the first submission have been addressed.

C. EU APPLICATION FORM

13. The EU application form, duly completed.

D. PROTOCOL

14. The protocol shall describe the objective, design, methodology, statistical considerations, purpose and organisation of the clinical trial.

15. The protocol shall be identified by:

(a) the title of the clinical trial;

(b) the EU trial number;

(c) the sponsor's protocol code number specific for all versions of it (if relevant);

(d) the date and number of the version, to be updated when it is amended;

(e) a short title or name assigned to the protocol; and

(f) the name and address of the sponsor, as well as the name and function of the representative or representatives of the sponsor authorised to sign the protocol or any substantial modification to the protocol.

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16. The protocol shall, when possible, be written in an easily accessible and searchable format, rather than scanned images.

17. The protocol shall at least include:

(a) a statement that the clinical trial is to be conducted in compliance with the protocol, with this Regulation and with the principles of good clinical practice;

(b) a comprehensive list of all investigational medicinal products and of all auxiliary medicinal products;

(c) a summary of findings from non-clinical studies that potentially have clinical significance and from other clinical trials that are relevant to the clinical trial;

(d) a summary of the known and potential risks and benefits including an evaluation of the anticipated benefits and risks to allow assessment in accordance with Article 6; for subjects in a clinical trial in an emergency situation, the scientific grounds for expecting that the participation of the subjects has the potential to produce a direct clinically relevant benefit shall be documented;

(e) where patients were involved in the design of the clinical trial, a description of their involvement;

(f) a description of, and justification for, the dosage, the dosage regime, the route and mode of administration, and the treatment period for all investigational medicinal products and auxiliary medicinal products;

(g) a statement of whether the investigational medicinal products and auxiliary medicinal products used in the clinical trial are authorised; if authorised, whether they are to be used in the clinical trial in accordance with the terms of their marketing authorisations, and, if not authorised, a justification for the use of non-authorised auxiliary medicinal products in the clinical trial;

(h) a description of the groups and subgroups of the subjects participating in the clinical trial, including, where relevant, groups of subjects with specific needs, for example. age, gender, participation of healthy volunteers, subjects with rare and ultra rare diseases;

(i) references to literature and data that are relevant to the clinical trial, and that provide background for the clinical trial;

(j) a discussion of the relevance of the clinical trial in order to allow assessment in accordance with Article 6;

(k) a description of the type of clinical trial to be conducted and a discussion of the trial design (including a schematic diagram of trial design, procedures and stages, if relevant);

(l) a specification of the primary end-points and the secondary end-points, if any, to be measured during the clinical trial;

(m) a description of the measures taken to minimise bias, including, if applicable, randomisation and blinding;

(n) a description of the expected duration of subject participation and a description of the sequence and duration of all clinical trial periods, including follow-up, if relevant;

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(o) a clear and unambiguous definition of the end of the clinical trial in question and, if it is not the date of the last visit of the last subject, a specification of the estimated end date and a justification thereof;

(p) a description of the criteria for discontinuing parts of the clinical trial or the entire clinical trial;

(q) arrangements for the maintenance of clinical trial treatment randomisation codes and procedures for breaking codes, if relevant;

(r) a description of procedures for the identification of data to be recorded directly on the Case Report Forms considered as source data;

(s) a description of the arrangements to comply with the applicable rules for the collection, storage and future use of biological samples from clinical trial subjects, where applicable, unless contained in a separate document;

(t) a description of the arrangements for tracing, storing, destroying and returning the investigational medicinal product and unauthorised auxiliary medicinal product in accordance with Article 51;

(u) a description of the statistical methods to be employed, including, if relevant:

— timing of any planned interim analysis and the number of subjects planned to be enrolled;

— reasons for choice of sample size;

— calculations of the power of the clinical trial and clinical relevance;

— the level of significance to be used;

— criteria for the termination of the clinical trial;

— procedures for accounting for missing, unused, and spurious data and for reporting any deviation from the original statistical plan; and

— the selection of subjects to be included in the analyses;

(v) a description of the subject inclusion and exclusion criteria, including criteria for withdrawing individual subjects from treatment or from the clinical trial;

(w) a description of procedures relating to the withdrawal of subjects from treatment or from the clinical trial including procedures for the collection of data regarding withdrawn subjects, procedures for replacement of subjects and the follow-up of subjects that have withdrawn from treatment or from the clinical trial;

(x) a justification for including subjects who are incapable of giving informed consent or other special populations, such as minors;

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(y) a justification for the gender and age allocation of subjects and, if a specific gender or age group is excluded from or underrepresented in the clinical trials, an explanation of the reasons and justification for these exclusion criteria;

(z) a detailed description of the recruitment and informed consent procedure, especially when subjects are incapable of giving informed consent;

(aa) a description of the treatments, including medicinal products, which are permitted or not permitted, before or during the clinical trial;

(ab) a description of the accountability procedures for the supply and administration of medicinal products to subjects including the maintenance of blinding, if applicable;

(ac) a description of procedures for monitoring subject compliance, if applicable;

(ad) a description of arrangements for monitoring the conduct of the clinical trial;

(ae) a description of the arrangements for taking care of the subjects after their participation in the clinical trial has ended, where such additional care is necessary because of the subjects' participation in the clinical trial and where it differs from that normally expected for the medical condition in question;

(af) a specification of the efficacy and safety parameters as well as the methods and timing for assessing, recording, and analysing these parameters;

(ag) a description of ethical considerations relating to the clinical trial if those have not been described elsewhere;

(ah) a statement from the sponsor (either in the protocol or in a separate document) confirming that the investigators and institutions involved in the clinical trial are to permit clinical trial-related monitoring, audits and regulatory inspections, including provision of direct access to source data and documents;

(ai) a description of the publication policy;

(aj) duly substantiated reasons for the submission of the summary of the results of the clinical trials after more than one year;

(ak) a description of the arrangements to comply with the applicable rules on the protection of personal data; in particular organisational and technical arrangements that will be implemented to avoid unauthorised access, disclosure, dissemination, alteration or loss of information and personal data processed;

(al) a description of measures that will be implemented to ensure confidentiality of records and personal data of subjects;

(am) a description of measures that will be implemented in case of data security breach in order to mitigate the possible adverse effects.

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

19. With regard to the notification of adverse events, the protocol shall identify the categories of:

    (a) adverse events or laboratory anomalies that are critical to safety evaluations and must be reported by the investigator to the sponsor, and

    (b) serious adverse events which do not require immediate reporting by the investigator to the sponsor.

20. The protocol shall describe the procedures for:

    (a) eliciting and recording adverse events by the investigator, and the reporting of relevant adverse events by the investigator to the sponsor;

    (b) reporting by the investigator to the sponsor of those serious adverse events which have been identified in the protocol as not requiring immediate reporting;

    (c) reporting of suspected unexpected serious adverse reactions by the sponsor to the Eudravigilance database; and

    (d) follow-up of subjects after adverse reactions including the type and duration of follow-up.

21. In case the sponsor intends to submit a single safety report on all investigational medicinal products used in the clinical trial in accordance with Article 43(2), the protocol shall indicate the reasons thereof.

22. Issues regarding labelling and the unblinding of investigational medicinal products shall be addressed in the protocol, where necessary.

23. The protocol shall be accompanied by the Charter of the Data Safety Monitoring Committee, if applicable.

24. The protocol shall be accompanied by a synopsis of the protocol.

E. INVESTIGATOR'S BROCHURE (IB)

25. An IB, which has been prepared in accordance with the state of scientific knowledge and international guidance, shall be submitted.

26. The purpose of the IB is to provide the investigators and others involved in the clinical trial with information to facilitate their understanding of the rationale for, and their compliance with, key features of the protocol, such as the dose, dose frequency/interval, methods of administration, and safety monitoring procedures.

27. The information in the IB shall be presented in a concise, simple, objective, balanced and non-promotional form that enables a clinician or investigator to understand it and make an unbiased risk-benefit assessment of the appropriateness of the proposed clinical trial. It shall be prepared from all available information and evidence that

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supports the rationale for the proposed clinical trial and the safe use of the investigational medicinal product in the clinical trial and be presented in the form of summaries.

28. If the investigational medicinal product is authorised, and is used in accordance with the terms of the marketing authorisation, the approved summary of product characteristics (SmPC) shall be the IB. If the conditions of use in the clinical trial differ from those authorised, the SmPC shall be supplemented with a summary of relevant non-clinical and clinical data that support the use of the investigational medicinal product in the clinical trial. Where the investigational medicinal product is identified in the protocol only by its active substance, the sponsor shall select one SmPC as equivalent to the IB for all medicinal products that contain that active substance and are used at any clinical trial site.

29. For a multinational clinical trial where the medicinal product to be used in each Member State concerned is authorised at national level, and the SmPC varies among Member States concerned, the sponsor shall choose one SmPC for the whole clinical trial. This SmPC shall be the one best suited to ensure patient safety.

30. If the IB is not an SmPC, it shall contain a clearly identifiable section called the 'Reference Safety Information' (RSI). In accordance with paragraphs 10 and 11 of Annex III, the RSI shall contain product information on the investigational medicinal product and on how to determine what adverse reactions are to be considered as expected adverse reactions, and on the frequency and nature of those adverse reactions.

F. DOCUMENTATION RELATING TO COMPLIANCE WITH GOOD MANUFACTURING PRACTICE (GMP) FOR THE INVESTIGATIONAL MEDICINAL PRODUCT

31. As regards documentation relating to GMP compliance, the following shall apply.

32. No documentation needs to be submitted where the investigational medicinal product is authorised and is not modified, whether or not it is manufactured in the Union.

33. If the investigational medicinal product is not authorised, and does not have a marketing authorisation from a third country that is party to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and is not manufactured in the Union, the following documentation shall be submitted:

(a) a copy of the authorisation referred to in Article 61; and

(b) certification by the qualified person in the Union that the manufacturing complies with GMP at least equivalent to the GMP in the Union, unless there are specific arrangements provided for in mutual recognition agreements between the Union and third countries.

34. In all other cases, a copy of the authorisation referred to in Article 61 shall be submitted.

35. For processes related to investigational medicinal products set out in Article 61(5), which are not subject to an authorisation in accordance with Article 61, documentation to demonstrate compliance with the requirements referred to in Article 61(6) shall be submitted.

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G. INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER (IMPD)

36. The IMPD shall give information on the quality of any investigational medicinal product, the manufacture and control of the investigational medicinal product, and data from non-clinical studies and from its clinical use.

1.1. **Data relating to the investigational medicinal product**

Introduction

37. Regarding data, the IMPD may be replaced by other documentation which may be submitted alone or with a simplified IMPD. The details of this 'simplified IMPD' are set out in section 1.2 'Simplified IMPD by referring to other documentation'.

38. Each section of the IMPD shall be prefaced with a detailed table of contents and a glossary of terms.

39. The information in the IMPD shall be concise. The IMPD must not be unnecessarily voluminous. It is preferable to present data in tabular form accompanied by a brief narrative highlighting the main salient points.

Quality data

40. Quality data shall be submitted in a logical structure such as that of Module 3 of the ICH Common Technical Document format.

Non-clinical pharmacology and toxicology data

41. The IMPD shall also contain summaries of non-clinical pharmacology and toxicology data for any investigational medicinal product used in the clinical trial in accordance with international guidance. It shall contain a reference list of studies conducted and appropriate literature references. Wherever appropriate, it is preferable to present data in tabular form accompanied by a brief narrative highlighting the main salient points. The summaries of the studies conducted shall allow an assessment of the adequacy of the study and whether the study has been conducted according to an acceptable protocol.

42. Non-clinical pharmacology and toxicology data shall be submitted in a logical structure, such as that of Module 4 of the ICH Common Technical Document format.

43. The IMPD shall provide a critical analysis of the data, including justification for omissions of data, and an assessment of the safety of the product in the context of the proposed clinical trial rather than a mere factual summary of the studies conducted.

44. The IMPD shall contain a statement of the good laboratory practice status or equivalent standards, as referred to in Article 25(3).

45. The test material used in toxicity studies shall be representative of that of the clinical trial use in terms of qualitative and quantitative impurity profiles. The preparation of the test material shall be subject to the controls necessary to ensure this and thus support the validity of the study.

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Data from previous clinical trials and human experience

46. Data from previous clinical trials and human experience shall be submitted in a logical structure, such as that of Module 5 of the ICH Common Technical Document format.

47. This section shall provide summaries of all available data from previous clinical trials and human experience with the investigational medicinal products.

It shall also contain a statement of the compliance with good clinical practice of those previous clinical trials, as well as a reference to the public entry referred to in Article 25(6).

Overall risk and benefit assessment

48. This section shall provide a brief integrated summary that critically analyses the non-clinical and clinical data in relation to the potential risks and benefits of the investigational medicinal product in the proposed clinical trial unless this information is already provided in the protocol. In the latter case, it shall cross-refer to the relevant section in the protocol. The text shall identify any studies that were terminated prematurely and discuss the reasons. Any evaluation of foreseeable risks and anticipated benefits for studies on minors or incapacitated adults shall take account of the specific provisions set out in this Regulation.

49. Where appropriate, safety margins shall be discussed in terms of relative systemic exposure to the investigational medicinal product, preferably based on 'area under the curve' (AUC) data, or peak concentration (C_{max}) data, whichever is considered more relevant, rather than in terms of applied dose. The clinical relevance of any findings in the non-clinical and clinical studies along with any recommendations for further monitoring of effects and safety in the clinical trials shall also be discussed.

1.2. **Simplified IMPD by referring to other documentation**

50. The applicant may refer to other documentation submitted alone or with a simplified IMPD.

Possibility of referring to the IB

51. The applicant may either provide a stand-alone IMPD or cross-refer to the IB for the reference safety information and the summaries of pre-clinical and clinical parts of the IMPD. In the latter case, the summaries of pre-clinical information and clinical information shall include data, preferably in tables, providing sufficient detail to allow assessors to reach a decision on the potential toxicity of the investigational medicinal product and the safety of its use in the proposed clinical trial. If there is some special aspect of the pre-clinical data or clinical data that requires a detailed expert explanation or discussion beyond what would usually be included in the IB, the pre-clinical and clinical information shall be submitted as part of the IMPD.

Possibility of referring to the SmPC

52. The applicant may submit the version of the SmPC valid at the time of application, as the IMPD if the investigational medicinal product is authorised. The exact requirements are detailed in Table 1. Where new data are provided, it should be clearly identified.

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Table 1: Content of the simplified IMPD

Types of previous assessment	Quality data	Non-clinical data	Clinical data
The investigational medicinal product is authorised or has a marketing authorisation in an ICH country and is used in the clinical trial:			
— within the conditions of the SmPC	SmPC		
— outside the conditions of the SmPC	SmPC	If appropriate	If appropriate
— after modification (for example blinding)	P+A	SmPC	SmPC
Another pharmaceutical form or strength of the investigational medicinal product is authorised or has a marketing authorisation in an ICH country and the investigational medicinal product is supplied by the marketing authorisation holder	SmPC+P+A	Yes	Yes
The investigational medicinal product is not authorised and has no marketing authorisation in an ICH country but the active substance is contained in an authorised medicinal product, and			
— is supplied by the same manufacturer	SmPC+P+A	Yes	Yes
— is supplied by another manufacturer	SmPC+S+P+A	Yes	Yes
The investigational medicinal product was subject to a previous clinical trial application and authorised in the Member State concerned and has not been modified, and			
— no new data are available since last amendment to the clinical trial application,	Reference to previous submission		
— new data are available since last amendment to the clinical trial application,	New data	New data	New data
— is used under different conditions	If appropriate	If appropriate	If appropriate

(S: Data relating to the active substance; P: Data relating to the investigational medicinal product; A: Additional information on Facilities and Equipment, Adventitious Agents Safety Evaluation, Novel Excipients, and Solvents for Reconstitution and Diluents)

53. If the investigational medicinal product is defined in the protocol in terms of active substance or ATC code (see above, paragraph 18), the applicant may replace the IMPD by one representative SmPC for each active substance/active substance pertaining to that ATC group. Alternatively, the applicant may provide a collated document containing information equivalent to that in the representative SmPCs for each active substance that could be used as an investigational medicinal product in the clinical trial.

1.3. **IMPD in cases of placebo**

54. If the investigational medicinal product is a placebo, the information requirements shall be limited to quality data. No additional documentation is required if the placebo has the same composition as the tested investigational medicinal product (with the exception of the active substance), is manufactured by the same manufacturer, and is not sterile.

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H. AUXILIARY MEDICINAL PRODUCT DOSSIER

55. Without prejudice to Article 65, the documentation requirements set out in sections F and G shall also apply to auxiliary medicinal products. However, where the auxiliary medicinal product is authorised in the Member State concerned, no additional information is required.

I. SCIENTIFIC ADVICE AND PAEDIATRIC INVESTIGATION PLAN (PIP)

56. If available, a copy of the summary of scientific advice of the Agency, or of any Member State or third country, with regard to the clinical trial shall be submitted.

57. If the clinical trial is part of an agreed PIP, a copy of the Agency's decision on the agreement on the PIP, and the opinion of the Paediatric Committee, unless these documents are fully accessible via the internet shall be submitted. In the latter case, a link to this documentation in the cover letter is sufficient (see section B).

J. CONTENT OF THE LABELLING OF THE INVESTIGATIONAL MEDICINAL PRODUCTS

58. A description of the content of the labelling of the investigational medicinal product in accordance with Annex VI shall be provided.

K. RECRUITMENT ARRANGEMENTS (INFORMATION PER MEMBER STATE CONCERNED)

59. Unless described in the protocol, a separate document shall describe in detail the procedures for inclusion of subjects and shall provide a clear indication of what the first act of recruitment is.

60. Where the recruitment of subjects is done through advertisement, copies of the advertising material shall be submitted, including any printed materials, and audio or visual recordings. The procedures proposed for handling responses to the advertisement shall be outlined. This includes copies of communications used to invite subjects to participate in the clinical trial and arrangements for information or advice to the respondents found not to be suitable for inclusion in the clinical trial.

L. SUBJECT INFORMATION, INFORMED CONSENT FORM AND INFORMED CONSENT PROCEDURE (INFORMATION PER MEMBER STATE CONCERNED)

61. All information given to the subjects (or, where applicable, to their legally designated representatives) before their decision to participate or abstain from participation shall be submitted together with the form for written informed consent, or other alternative means according to Article 29(1) for recording informed consent.

62. A description of procedures relating to informed consent for all subjects, and in particular:

(a) in clinical trials with minors or incapacitated subjects, the procedures to obtain informed consent from the legally designated representatives, and the involvement of the minor or incapacitated subject shall be described;

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(b) if a procedure with consent witnessed by an impartial witness is to be used, relevant information on the reason for using an impartial witness, on the selection of the impartial witness and on the procedure for obtaining informed consent shall be provided;

(c) in the case of clinical trials in emergency situations as referred to in Article 35, the procedure for obtaining the informed consent of the subject or the legally designated representative to continue the clinical trial shall be described;

(d) in the case of clinical trials in emergency situations as referred to in Article 35, the description of the procedures followed to identify the urgency of the situation and to document it;

(e) in the case of clinical trials where their methodology requires that groups of subjects rather than individual subjects are allocated to receive different investigational medicinal products, as referred to in Article 30, and where, as a consequence, simplified means for obtaining informed consent will be used, the simplified means shall be described.

63. In the cases set out in paragraph 62, the information given to the subject and to his or her legally designated representative shall be submitted.

M. SUITABILITY OF THE INVESTIGATOR (INFORMATION PER MEMBER STATE CONCERNED)

64. A list of the planned clinical trial sites, the name and position of the principal investigators and the planned number of subjects at the sites shall be submitted.

65. Description of the qualification of the investigators in a current curriculum vitae and other relevant documents shall be submitted. Any previous training in the principles of good clinical practice or experience obtained from work with clinical trials and patient care shall be described.

66. Any conditions, such as economic interests and institutional affiliations, that might influence the impartiality of the investigators shall be presented.

N. SUITABILITY OF THE FACILITIES (INFORMATION PER MEMBER STATE CONCERNED)

67. A duly justified written statement on the suitability of the clinical trial sites adapted to the nature and use of the investigational medicinal product and including a description of the suitability of facilities, equipment, human resources and description of expertise, issued by the head of the clinic/institution at the clinical trial site or by some other responsible person, according to the system in the Member State concerned, shall be submitted.

O. PROOF OF INSURANCE COVER OR INDEMNIFICATION (INFORMATION PER MEMBER STATE CONCERNED)

68. Proof of insurance, a guarantee, or a similar arrangement shall be submitted, if applicable.

P. FINANCIAL AND OTHER ARRANGEMENTS (INFORMATION PER MEMBER STATE CONCERNED)

69. A brief description of the financing of the clinical trial.

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70. Information on financial transactions and compensation paid to subjects and investigator/site for participating in the clinical trial shall be submitted.

71. Description of any other agreement between the sponsor and the site shall be submitted.

Q. PROOF OF PAYMENT OF FEE (INFORMATION PER MEMBER STATE CONCERNED)

72. Proof of payment shall be submitted, if applicable.

R. PROOF THAT DATA WILL BE PROCESSED IN COMPLIANCE WITH UNION LAW ON DATA PROTECTION

73. A statement by the sponsor or his or her representative that data will be collected and processed in accordance with Directive 95/46/EEC shall be provided.

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ANNEX II

APPLICATION DOSSIER FOR SUBSTANTIAL MODIFICATION

A. INTRODUCTION AND GENERAL PRINCIPLES

1. Where a substantial modification concerns more than one clinical trial of the same sponsor and the same investigational medicinal product, the sponsor may make a single request for authorisation of the substantial modification. The cover letter shall contain a list of all clinical trials to which the application for substantial modification relates, with the EU trial numbers and respective modification code numbers of each of those clinical trials.

2. The application shall be signed by the sponsor or a representative of the sponsor. This signature shall confirm that the sponsor is satisfied that:

   (a) the information provided is complete;

   (b) the attached documents contain an accurate account of the information available; and

   (c) the clinical trial will be conducted in accordance with the amended documentation.

B. COVER LETTER

3. A cover letter with the following information:

   (a) in its subject line, the EU trial number with the title of the clinical trial and the substantial modification code number which allows unique identification of the substantial modification, and which shall be used consistently throughout the application dossier;

   (b) identification of the applicant;

   (c) identification of the substantial modification (the sponsor's substantial modification code number and date), whereby the modification may refer to several changes in the protocol or scientific supporting documents;

   (d) a highlighted indication of any special issues relating to the modification and an indication as to where the relevant information or text is located in the original application dossier;

   (e) identification of any information not contained in the modification application form that might impact on the risk to subjects; and

   (f) where applicable, a list of all clinical trials which are substantially modified, with EU trial numbers and respective modification code numbers.

C. MODIFICATION APPLICATION FORM

4. The modification application form, duly completed.

D. DESCRIPTION OF THE MODIFICATION

5. The modification shall be presented and described as follows:

   (a) an extract from the documents to be amended showing previous and new wording in track changes, as well as an extract showing only the new wording, and a explanation of the changes; and

   (b) notwithstanding point (a), if the changes are so widespread or far-reaching that they justify an entirely new version of the document, a new version of the entire document (in such cases, an additional table lists the amendments to the documents, whereby identical changes can be grouped).

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6. The new version of the document shall be identified by the date and an updated version number.

E. SUPPORTING INFORMATION

7. Where applicable, additional supporting information shall at least include:

(a) summaries of data;

(b) an updated overall risk/benefit assessment;

(c) possible consequences for subjects already included in the clinical trial;

(d) possible consequences for the evaluation of the results;

(e) documents which relate to any changes to the information provided to subjects or their legally designated representatives, the informed consent procedure, informed consent forms, information sheets, or to letters of invitation; and

(f) a justification for the changes sought in the application for a substantial modification.

F. UPDATE OF EU APPLICATION FORM

8. If a substantial modification involves changes to entries on the EU application form referred to in Annex I, a revised version of that form shall be submitted. The fields affected by the substantial modification shall be highlighted in the revised form.

G. PROOF OF PAYMENT OF FEE (INFORMATION PER MEMBER STATE CONCERNED)

9. Proof of payment shall be submitted, if applicable.

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ANNEX III

SAFETY REPORTING

1. REPORTING OF SERIOUS ADVERSE EVENTS BY THE INVESTIGATOR TO THE SPONSOR

1. The investigator does not need to actively monitor subjects for adverse events once the clinical trial has ended with regard to the subjects treated by him, unless otherwise provided for in the protocol.

2. REPORTING OF SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSARS) BY THE SPONSOR TO THE AGENCY IN ACCORDANCE WITH ARTICLE 42

2.1. **Adverse Events and Causality**

2. Medication errors, pregnancies and uses outside what is foreseen in the protocol, including misuse and abuse of the product, shall be subject to the same obligation to report as adverse reactions.

3. In determining whether an adverse event is an adverse reaction, consideration shall be given to whether there is a reasonable possibility of establishing a causal relationship between the event and the investigational medicinal product based on an analysis of available evidence.

4. In the absence of information on causality provided by the reporting investigator, the sponsor shall consult the reporting investigator and encourage him to express an opinion on this issue. The causality assessment given by the investigator shall not be downgraded by the sponsor. If the sponsor disagrees with the investigator's causality assessment, the opinion of both the investigator and the sponsor shall be provided with the report.

2.2. **Expectedness, unexpectedness and the RSI**

5. In determining whether an adverse event is unexpected, consideration shall be given to whether the event adds significant information on the specificity, increase of occurrence, or severity of a known, already documented serious adverse reaction.

6. The expectedness of an adverse reaction shall be set out by the sponsor in the RSI. Expectedness shall be determined on the basis of events previously observed with the active substance and not on the basis of the anticipated pharmacological properties of a medicinal product or events related to the subject's disease.

7. The RSI shall be contained in the SmPC or the IB. The covering letter shall refer to the location of the RSI in the application dossier. If the investigational medicinal product is authorised in several Member States concerned with different SmPCs, the sponsor shall select the most appropriate SmPC, with reference to subject safety, as the RSI.

8. The RSI may change during the conduct of a clinical trial. For the purpose of reporting SUSARs the version of the RSI at the moment of occurrence of the SUSAR shall apply. Thus, a change of the RSI impacts on the number of adverse reactions to be reported as SUSARs. Regarding the applicable RSI for the purpose of the annual safety report, see section 3 of this Annex.

9. If information on expectedness has been provided by the reporting investigator, this shall be taken into consideration by the sponsor.

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2.3. **Information for the reporting of SUSARs**

10. The information shall at least include:

(a) a valid EU trial number;

(b) a sponsor study number;

(c) an identifiable coded subject;

(d) an identifiable reporter;

(e) a SUSAR;

(f) a suspect investigational medicinal product (including active substance name-code);

(g) a causality assessment.

11. In addition, in order to properly process the report electronically, the following administrative information shall be provided:

(a) the sender's (case) safety report unique identifier;

(b) the receive date of the initial information from the primary source;

(c) the receipt date of the most recent information;

(d) the worldwide unique case identification number;

(e) the sender identifier.

2.4. **Follow-up reports of SUSARs**

12. If the initial report of a SUSAR referred to in point (a) of Article 42(2) (fatal or life-threatening) is incomplete, for example if the sponsor has not provided all the information within seven days, the sponsor shall submit a completed report based on the initial information within an additional eight days.

13. The clock for initial reporting (day 0 = Di 0) starts as soon as the information containing the minimum reporting criteria has been received by the sponsor.

14. If significant new information on an already reported case is received by the sponsor, the clock starts again at day zero, that is the date of receipt of the new information. This information shall be reported as a follow-up report within 15 days.

15. If the initial report of a SUSAR referred to in Article 42(2)(c) (initially considered to be non-fatal or non-life-threatening but which turns out to be fatal or life-threatening) is incomplete, a follow-up report shall be made as soon as possible, but within a maximum of seven days of first knowledge of the reaction being fatal or life-threatening. The sponsor shall submit a completed report within an additional eight days.

16. In cases where a SUSAR turns out to be fatal or life-threatening, whereas initially it was considered as non-fatal or not life-threatening, if the initial report has not yet been submitted, a combined report shall be created.

2.5. **Unblinding treatment allocation**

17. The investigator shall only unblind the treatment allocation of a subject in the course of a clinical trial if unblinding is relevant to the safety of the subject.

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18. When reporting a SUSAR to the Agency, the sponsor shall only unblind the treatment allocation of the affected subject to whom the SUSAR relates.

19. If an event is potentially a SUSAR the blind shall be broken for that subject only by the sponsor. The blind shall be maintained for other persons responsible for the ongoing conduct of the clinical trial (such as the management, monitors, investigators) and those persons responsible for data analysis and interpretation of results at the conclusion of the clinical trial, such as biometrics personnel.

20. Unblinded information shall be accessible only to persons who need to be involved in the safety reporting to the Agency, to Data Safety Monitoring Boards ('DSMB'), or to persons performing ongoing safety evaluations during the clinical trial.

21. However, for clinial trials carried out in high morbidity or high mortality disease, where efficacy end-points could also be SUSARs or when mortality or another 'serious' outcome, that may potentially be reported as a SUSAR, is the efficacy end-point in a clinical trial, the integrity of the clinical trial may be compromised if the blind is systematically broken. Under these and similar circumstances, the sponsor shall highlight in the protocol which serious events are to be treated as disease-related and are not subject to systematic unblinding and expedited reporting.

22. If following unblinding, an event turns out to be a SUSAR the reporting rules for SUSARs set out in Article 42 and in Section 2 of this Annex shall apply.

3. ANNUAL SAFETY REPORTING BY THE SPONSOR

23. The report shall contain, in an appendix, the RSI in effect at the start of the reporting period.

24. The RSI in effect at the start of the reporting period shall serve as RSI during the reporting period.

25. If there are significant changes to the RSI during the reporting period they shall be listed in the annual safety report. Moreover, in this case the revised RSI shall be submitted as an appendix to the report, in addition to the RSI in effect at the start of the reporting period. Despite the change to the RSI, the RSI in effect at the start of the reporting period serves as RSI during the reporting period.

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ANNEX IV

CONTENT OF THE SUMMARY OF THE RESULTS OF THE CLINICAL TRIAL

The summary of the results of the clinical trial shall contain information on the following elements:

A. CLINICAL TRIAL INFORMATION:

1. Clinical trial identification (including title of the trial and protocol number);

2. Identifiers (including EU trial number, other identifiers);

3. Sponsor details (including scientific and public contact points);.

4. Paediatric regulatory details (including information whether the clinical trial is a part of a Paediatric Investigation Plan);

5. Result analysis stage (including information about intermediate data analysis date, interim or final analysis stage, date of global end of the clinical trial). For clinical trials replicating studies on already authorised investigational medicinal products and used in accordance with the terms of the marketing authorisation, the summary of the results should also indicate identified concerns in the overall results of the clinical trial relating to relevant aspects of the efficacy of the related medicinal product;

6. General information about the clinical trial (including information about main objectives of the trial, trial design, scientific background and explanation of rationale for the trial; date of the start of the trial, measures of protection of subjects taken, background therapy; and statistical methods used);

7. Population of subjects (including information with actual number of subjects included in the clinical trial in the Member State concerned, in the Union and in third countries; age group breakdown, gender breakdown).

B. SUBJECT DISPOSITION:

1. Recruitment (including information on the number of subjects screened, recruited and withdrawn; inclusion and exclusion criteria; randomisation and blinding details; investigational medicinal products used);

2. Pre-assignment Period;

3. Post Assignment Periods.

C. BASELINE CHARACTERISTICS:

1. Baseline Characteristics (Required) Age;

2. Baseline Characteristics (Required) Gender;

3. Baseline Characteristics (Optional) Study Specific Characteristic.

D. END POINTS:

1. End point definitions ([1])

2. End Point #1

Statistical Analyses

([1]) Information shall be provided for as many end points as defined in the protocol.

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3. End Point #2

Statistical Analyses

E. ADVERSE EVENTS:

1. Adverse events information;

2. Adverse event reporting group;

3. Serious adverse event;

4. Non-serious adverse event.

F. ADDITIONAL INFORMATION:

1. Global Substantial Modifications;

2. Global Interruptions and re-starts;

3. Limitations, addressing sources of potential bias and imprecisions and Caveats;

4. A declaration by the submitting party on the accuracy of the submitted information.

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ANNEX V

CONTENT OF THE SUMMARY OF THE RESULTS OF THE CLINICAL TRIAL FOR LAYPERSONS

The summary of the results of the clinical trial for laypersons shall contain information on the following elements:

1. Clinical trial identification (including title of the trial, protocol number, EU trial number and other identifiers);

2. Name and contact details of the sponsor;

3. General information about the clinical trial (including where and when the trial was conducted, the main objectives of the trial and an explanation of the reasons for conducting it);

4. Population of subjects (including information on the number of subjects included in the trial in the Member State concerned, in the Union and in third countries; age group breakdown and gender breakdown; inclusion and exclusion criteria);

5. Investigational medicinal products used;

6. Description of adverse reactions and their frequency;

7. Overall results of the clinical trial;

8. Comments on the outcome of the clinical trial;

9. Indication if follow up clinical trials are foreseen;

10. Indication where additional information could be found.

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ANNEX VI

LABELLING OF INVESTIGATIONAL MEDICINAL PRODUCTS AND AUXILIARY MEDICINAL PRODUCTS

A. UNAUTHORISED INVESTIGATIONAL MEDICINAL PRODUCTS

A.1. **General rules**

1. The following particulars shall appear on the immediate and the outer packaging:

   (a) name, address and telephone number of the main contact for information on the product, clinical trial and emergency unblinding; this may be the sponsor, contract research organisation or investigator (for the purpose of this Annex this is referred to as the 'main contact');

   (b) the name of the substance and its strength or potency, and in the case of blind clinical trials the name of the substance is to appear with the name of the comparator or placebo on the packaging of both the unauthorised investigational medicinal product and the comparator or placebo;

   (c) pharmaceutical form, route of administration, quantity of dosage units;

   (d) the batch or code number identifying the contents and packaging operation;

   (e) a clinical trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;

   (f) the subject identification number and/or the treatment number and, where relevant, the visit number;

   (g) the name of the investigator (if not included in (a) or (e));

   (h) directions for use (reference may be made to a leaflet or other explanatory document intended for the subject or person administering the product);

   (i) 'For clinical trial use only' or similar wording;

   (j) the storage conditions;

   (k) period of use (expiry date or re-test date as applicable), in month and year format and in a manner that avoids any ambiguity; and

   (l) 'Keep out of reach of children', except when the product is for use in trials where the product is not taken home by subjects.

2. Symbols or pictograms may be included to clarify certain information mentioned above. Additional information, warnings or handling instructions may be displayed.

3. The address and telephone number of the main contact shall not be required to appear on the label if subjects have been given a leaflet or card which provides these details and have been instructed to keep this in their possession at all times.

A.2. **Limited labelling of immediate packaging**

A.2.1. *Immediate and outer packaging provided together*

4. When the product is provided to the subject or the person administering the medicinal product in an immediate packaging and outer packaging intended to remain together, and the outer packaging carries

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the particulars listed in section A.1., the following particulars shall appear on the immediate packaging (or any sealed dosing device that contains the immediate package):

(a) name of the main contact;

(b) pharmaceutical form, route of administration (may be excluded for oral solid dose forms), quantity of dosage units and, in the case of clinical trials which do not involve the blinding of the label, the name/identifier and strength/potency;

(c) batch and/or code number identifying the contents and packaging operation;

(d) a clinical trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;

(e) the subject identification number and/or the treatment number and, where relevant, the visit number; and

(f) period of use (expiry date or re-test date as applicable), in month and year format and in a manner that avoids any ambiguity.

A.2.2. *Small immediate packaging*

5. If the immediate packaging takes the form of blister packs or small units such as ampoules on which the particulars required in section A.1. cannot be displayed, the outer packaging provided shall bear a label with those particulars. The immediate packaging shall contain the following:

(a) name of the main contact;

(b) route of administration (may be excluded for oral solid dose forms) and, in the case of clinical trials which do not involve the blinding of the label, the name/identifier and strength/potency;

(c) batch or code number identifying the contents and packaging operation;

(d) a clinical trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;

(e) the subject identification number/treatment number and, where relevant, the visit number; and

(f) period of use (expiry date or re-test date as applicable), in month and year format and in a manner that avoids any ambiguity.

B. UNAUTHORISED AUXILIARY MEDICINAL PRODUCTS

6. The following particulars shall appear on the immediate and the outer packaging:

(a) name of the main contact;

(b) name of the medicinal product, followed by its strength and pharmaceutical form;

(c) statement of the active substances expressed qualitatively and quantitatively per dosage unit;

(d) batch or code number identifying the contents and packaging operation;

(e) clinical trial reference code allowing identification of the clinical trial site, investigator and subject;

▼B

(f) directions for use (reference may be made to a leaflet or other explanatory document intended for the subject or person administering the product);

(g) 'For clinical trial use only' or similar wording;

(h) the storage conditions; and

(i) period of use (expiry date or retest date as applicable).

C. ADDITIONAL LABELLING FOR AUTHORISED INVESTIGATIONAL MEDICINAL PRODUCTS

7. In accordance with Article 67(2), the following particulars shall appear on the immediate and the outer packaging:

(a) name of the main contact;

(b) clinical trial reference code allowing identification of the clinical trial site, investigator, sponsor and subject;

(c) 'For clinical trial use only' or similar wording.

D. REPLACING OF INFORMATION

8. The particulars listed in sections A, B and C, other than those particulars listed in paragraph 9, may be omitted from the label of a product and made available by other means, for example by use of a centralised electronic randomisation system, use of a centralised information system, provided that the safety of the subject and the reliability and robustness of data are not compromised. This shall be justified in the protocol.

9. The particulars referred to in the following points shall not be omitted from the label of a product:

(a) paragraph 1, points (b), (c), (d), (f), (j) and (k);

(b) paragraph 4, points (b), (c), (e), and (f);

(c) paragraph 5, points (b), (c), (e), and (f);

(d) paragraph 6, points (b), (d), (e), (h), and (i).

▼B

ANNEX VII

CORRELATION TABLE

Directive 2001/20/EC	This Regulation
Article 1(1)	Article 1 and Article 2(1) and (2) points (1), (2) and (4)
Article 1(2)	Article 2(2) point (30)
Article 1(3), first subparagraph	—
Article 1(3), second subparagraph	Article 47, third subparagraph
Article 1(4)	Article 47, second subparagraph
Article 2	Article 2
Article 3(1)	—
Article 3(2)	Articles 4, 28, 29 and 76
Article 3(3)	Article 28(1)(f)
Article 3(4)	Article 28(1)(g)
Article 4	Articles 10(1), 28, 29 and 32
Article 5	Articles 10(2), 28, 29 and 31
Article 6	Articles 4 to 14
Article 7	Articles 4 to 14
Article 8	—
Article 9	Articles 4 to 14
Article 10(a)	Articles 15 to 24
Article 10(b)	Article 54
Article 10(c)	Articles 37 and 38
Article 11	Article 81
Article 12	Article 77
Article 13(1)	Article 61(1) to (4)
Article 13(2)	Article 61(2)
Article 13(3), first subparagraph	Articles 62(1) and 63(1) and (3)
Article 13(3), second subparagraph	Article 63(1)
Article 13(3), third subparagraph	—
Article 13(4)	Article 62
Article 13(5)	—
Article 14	Articles 66 to 70
Article 15(1)	Article 78(1), (2) and (5)
Article 15(2)	Article 78(6)

▼B

Directive 2001/20/EC	This Regulation
Article 15(3)	—
Article 15(4)	—
Article 15(5)	Articles 57, 58 and 78(7)
Article 16	Article 41
Article 17(1)(a) to (c)	Article 42
Article 17(1)(d)	—
Article 17(2)	Article 43
Article 17(3)(a)	—
Article 17(3)(b)	Article 44(1)
Article 18	—
Article 19, first paragraph, first sentence	Article 75
Article 19, first paragraph, second sentence	Article 74
Article 19, second paragraph	Article 92
Article 19, third paragraph	—
Article 20	—
Article 21	Article 88
Article 22	—
Article 23	—
Article 24	—