COMMISSION IMPLEMENTING REGULATION (EU) 2022/20

of 7 January 2022

laying down rules for the application of Regulation (EU) No 536/2014 of the European Parliament and of the Council as regards setting up the rules and procedures for the cooperation of the Member States in safety assessment of clinical trials

(Text with EEA relevance)

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to 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 ([1]), and in particular Article 44(2) thereof,

Whereas:

(1) Regulation (EU) No 536/2014 lays down the legal framework for the conduct of clinical trials on medicinal products for human use in the Union to ensure that the rights of subjects ('participants'), their safety and well-being are protected, and that the generated data are reliable and robust. In particular, while the overall responsibility for ensuring participants' safety lies with the sponsor of the clinical trial, it is reinforced by additional oversight from the Member States including through their cooperation in the assessment of the safety of the investigational medicinal products.

(2) Articles 42 and 43 of Regulation (EU) No 536/2014 provide that the sponsor of a clinical trial is to report suspected unexpected serious adverse reactions to investigational medicinal products used in the clinical trial and to submit annually safety reports to the European Medicines Agency ('the Agency') through the database referred to in Article 40(1) of that Regulation. The information reported under those provisions is to be forwarded by the Agency to the Member States concerned, which are to cooperate in the assessment of that information, with the involvement of the responsible ethics committee, where appropriate, in accordance with Article 44 of Regulation (EU) No 536/2014.

(3) Setting out a framework by laying down the rules for the cooperation between Member States in the assessment of information and reports submitted under Articles 42 and 43 of Regulation (EU) No 536/2014 reinforces safety harmonisation and increases scrutiny in safety oversight in the Union. This should strengthen participants' safety in clinical trials and contribute to improved data robustness regarding the safety profile of investigational medicinal products and their corresponding active substances.

(4) Oversight of the safety of active substances used as investigational medicinal products in clinical trials authorised in only one Member State (mono-national active substances), active substances in investigational medicinal products used as a reference, including as a placebo, and active substances used in auxiliary medicinal products should be outside the scope of this Regulation.

(5) To ensure effective and efficient cooperation between Member States in the assessment of information and reports, submitted under Articles 42 and 43 of Regulation (EU) No 536/2014, for each active substance used in investigational medicinal products, a Member State should be appointed to assess that information and those reports ('safety assessing Member State'), based on a fair division of workload between Member States and on existing expertise with the given active substance.

(6) Taking into account the considerable attrition of active substances over the development lifecycle and the fact that only a proportion of active substances will be investigated as multi-national active substances in the Union, safety related information for a mono-national active substance should be assessed by the reporting Member State. Those assessments by the reporting Member State should be recorded in a manner that ensures transparency and enables

([1]) OJ L 158, 27.5.2014, p. 1.

continuity in case an originally mono-national active substance becomes a multi-national active substance, for example through the extension of the clinical trial to another Member State or where another Member State has authorised a clinical trial that involves the same active substance. Once a mono-national active substance becomes multi-national, it should benefit from coordinated safety assessment.

(7) The selection of the first safety assessing Member State for an active substance for the safety cooperation is driven by the reporting Member State, referred to in Article 5 of Regulation (EU) No 536/2014, of the first clinical trial using this active substance in the Union. The reporting Member State should select the safety assessing Member State when more than one Member State, or no Member State at all, expresses interest in becoming the safety assessing Member State for an active substance.

(8) The tasks related to safety assessment should be distributed proportionally between the Member States. The workload associated with the safety oversight of an active substance may depend on, amongst others, existing knowledge with the safety of the active substance and risk adaptations in the screening frequency and the extent of the assessments.

(9) To maintain a proportionate distribution of work between Member States over time, it should be possible, upon request of the original safety assessing Member State, to transfer the role of safety assessing Member State when the original safety assessing Member State is no longer a Member State concerned in any clinical trial involving the use of an active substance or when its workload related to the role of safety assessing Member State becomes disproportionately high in comparison to the workload of the other Member States. However, it is necessary to ensure the continuity of the safety assessment at any time during the re-selection process of the safety assessing Member State.

(10) Safety assessing Member States should assess the information submitted as suspected unexpected serious adverse reactions, and information contained in annual safety reports, referred to in Articles 42 and 43 of Regulation (EU) No 536/2014. When safety concerns arise from those assessments, the safety assessing Member State should prepare general recommendations as regards the safety of the active substance to the reporting Member States and to the Member States concerned by clinical trials involving investigational medicinal products containing that active substance. This enables the relevant reporting Member States and Member States concerned to take appropriate and proportionate corrective measures and other actions for safety oversight related to the active substance, when this is necessary.

(11) In addition, reporting Member States may consider involving the safety assessing Member State in assessing applications for substantial modifications to the reference safety information, submitted in accordance with Article 16 of Regulation (EU) No 536/2014. Substantial modifications to the reference safety information may have implications for the determination of expectedness of serious adverse reactions and, by way of consequence, on the reporting of suspected unexpected serious adverse reactions. To determine the expectedness of serious adverse reactions in relation to an investigational medicinal product, it is therefore appropriate to establish a harmonised approach to safety assessment using, as a basis, a common reference document. The reporting Member State and Member States concerned will remain responsible for the assessment of any substantial modification to the reference safety information.

(12) To further strengthen oversight and harmonisation as well as to avoid that different safety assessing Member States assess different investigational medicinal products using the same active substance, a single safety assessing Member State should, whenever possible, assess the safety of all investigational medicinal products containing the same active substance, regardless of the pharmaceutical form and strength or indication investigated and regardless of whether they are used in several clinical trials managed by the same or different sponsors. Such coordinated approach to the

safety assessment based on the active substance rather than on the investigational medicinal product avoids duplication of efforts and at the same time provides the safety assessing Member States with sufficient context for its safety assessments. This approach is also in line with the relevant guideline on Development Safety Update Report of the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH E2F) that recommends a single safety update report for an active substance to promote comprehensive analysis.

(13) A risk-based approach should be taken as regards the frequency of screening of safety information, the extent of its assessment and the timelines of assessment and reporting. Risk adaptations should depend on the knowledge about the safety profile of the active substance. For example, active substances with a marketing authorisation in the Union may be screened less frequently in comparison to unauthorised active substances.

(14) Relevant information systems that are managed by the Agency, including the Clinical Trials Information System, the EudraVigilance Database and the EU Medicinal Product Dictionary, should support Member States' cooperation in assessing the safety of active substances used as investigational medicinal products in clinical trials. This would enable the integration of information on, and the cooperation in, the safety assessment of clinical trials, which will significantly contribute to strengthening the understanding of the safety of medicinal products that are planned to enter or are already available on the Union market.

(15) The Commission should be able to control whether Member States correctly supervise compliance with the rules set out for the coordinated safety assessment of the information submitted in the reports for suspected unexpected serious adverse reactions and in annual safety reports.

(16) The measures provided for in this Regulation are in accordance with the opinion of the Standing Committee on Medicinal Products for Human Use established by Directive 2001/83/EC of the European Parliament and of the Council ([2]).

(17) This Regulation should become applicable at the same time as Regulation (EU) No 536/2014,

HAS ADOPTED THIS REGULATION:

CHAPTER I

GENERAL PROVISIONS

Article 1

Subject matter and scope

1. This Regulation sets out the rules for the cooperation of Member States in:

(a) the selection of safety assessing Member States in accordance with Article 3;

(b) the assessment of information submitted on suspected unexpected serious adverse reactions and of information contained in annual safety reports in accordance with Articles 6 and 7;

(c) the development of recommendations for the reporting Member States, referred to in Article 5 of Regulation (EU) No 536/2014, and the Member States concerned, aimed at addressing safety concerns emerging from the assessments referred to in point (b) and suggesting corrective measures and other actions for safety oversight related to the active substance;

([2]) Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67).

(d) the involvement of the safety assessing Member States in the assessment of substantial modifications to the reference safety information in accordance with Article 5(1), point (c), and Article 9(2), point (c);

(e) the coordination between the reporting Member States and the Member States concerned in the implementation of recommended corrective measures and risk mitigating actions in accordance with Article 8;

(f) the cooperation between safety assessing Member States, reporting Member States and Member States concerned in clinical trials using the same active substance, in accordance with Articles 5, 8 and 9.

2. This Regulation applies to all active substances that are used in investigational medicinal products in clinical trials authorised in at least two Member States, in accordance with Article 8 of Regulation (EU) No 536/2014, regardless of whether the clinical trial in question was authorised under that Regulation or initially under Directive 2001/20/EC ([3]) and subsequently under Regulation (EU) No 536/2014.

3. This Regulation does not apply to mono-national active substances, to active substances in investigational medicinal products used as reference products, including as a placebo, or to active substances used in auxiliary medicinal products.

Article 2

Definitions

1. For the purposes of this Regulation, the definitions of 'medicinal product', 'active substance' and 'adverse reaction', set out in Article 1, points (2), (3a) and (11), of Directive 2001/83/EC, respectively, apply.

2. For the purposes of this Regulation, the following definitions also apply:

(a) 'Multi-national clinical trial' means a clinical trial for which the sponsor submitted an application dossier to more than one Member State through the EU portal.

(b) 'Reference safety information' means the safety information contained in the latest approved version of the clinical trial dossier, which serves as the basis to determine the expectedness of an adverse reaction by the sponsor.

(c) 'Safety assessing Member State' means the Member State that assesses the information submitted as suspected unexpected serious adverse reactions in accordance with Article 42 of Regulation (EU) No 536/2014, and the information contained in annual safety reports submitted in accordance with Article 43 of that Regulation, for clinical trials involving investigational medicinal products that contain the same active substance, regardless of the pharmaceutical form and strength or indication investigated and regardless of whether they are used in one or several clinical trials managed by the same or different sponsors.

(d) 'Lead safety assessing Member State' means the safety assessing Member State, which coordinates the safety assessments for different active substances in a clinical trial or for several clinical trials, performed by several safety assessing Member States.

(e) 'New active substance for safety cooperation' means an active substance, which has not been previously used in an investigational medicinal product in any clinical trial authorised in the Union under Regulation (EU) No 536/2014, and therefore does not have an assigned safety assessing Member State.

(f) 'Safety concern in relation to an investigational medicinal product' means information on the safety of the investigational medicinal product with potential negative impact on its benefit-risk ratio or with a public health implication.

([3]) Directive 2001/20/EC of 4 April 2001 of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (OJ L 121, 1.5.2001, p. 34).

(g) 'Mono-national active substance' means an active substance, which is used in an investigational medicinal product in clinical trial(s) authorised in only one Member State.

(h) 'Multi-national active substance' means an active substance, which is used in an investigational medicinal product in clinical trial(s) authorised in more than one Member State.

(i) 'Screening of suspected unexpected serious adverse reactions' means the systematic identification of suspected unexpected serious adverse reactions that require an assessment leading to a decision on the need to notify the reporting Member States and Member States concerned.

CHAPTER II

COORDINATED SAFETY ASSESSMENT

Article 3

Selection of the safety assessing Member State

1. A safety assessing Member State shall be selected for each active substance that is used in clinical trials authorised in the Union in accordance with Regulation (EU) No 536/2014, in each of the following situations:

(a) the sponsor submits to more than one Member State in accordance with Article 5 or 11 of Regulation (EU) No 536/2014 an application dossier for the authorisation of a clinical trial with a new active substance for safety cooperation and at least two Member States authorise that clinical trial in accordance with Article 8 of that Regulation;

(b) a substantial modification adding a new active substance for safety cooperation to a clinical trial is authorised in at least two Member States concerned in accordance with Articles 19 and 23, respectively, of Regulation (EU) No 536/2014;

(c) a mono-national active substance becomes a multi-national active substance.

2. In the situations described in paragraph 1, points (a) and (b), any Member State, whether or not it received the application referred to in those points, may express interest, through the IT tools as described in Article 11, to become the safety assessing Member State, within 7 days after the authorisation of the clinical trial or of the substantial modification in the second Member State concerned. If more than one Member State expresses interest, the reporting Member State selects the safety assessing Member State within 5 days from the end of the 7 days period referred to in the first sentence, taking into account the existing expertise of the Member States relating to the active substance and the fair division of workload between Member States. If no Member State expresses interest, the reporting Member State, within 12 days after the authorisation of the clinical trial or of the substantial modification in the second Member State concerned, shall appoint the safety assessing Member State from among the Member States concerned, taking into account the fair division of workload between them.

3. When the authorisation of a clinical trial or of a substantial modification adding an active substance to a clinical trial concerns an active substance for which a safety assessing Member State has already been appointed, that safety assessing Member State shall also be appointed as the safety assessing Member State for the new or modified clinical trial, irrespective of whether the application has been submitted by the same or a different sponsor. This shall also apply where the existing safety assessing Member State (i) is not a Member State concerned for the clinical trial, (ii) refused the clinical trial application, and (iii) received an application limited only to aspects covered by Part I of the assessment report referred to in Article 11 of Regulation (EU) No 536/2014, as well as (iv) when the clinical trial is no longer ongoing in its territory.

4. When an active substance, which is not used in any ongoing clinical trials in the Union, but had a safety assessing Member State in the past, is reintroduced through the authorisation of a new clinical trial or a substantial modification of a clinical trial, that safety assessing Member State shall be appointed as the safety assessing Member State for this active substance in the new or modified clinical trial.

5. The reporting Member State of the clinical trial shall verify if there is an existing safety assessing Member State for any active substance used in investigational medicinal products in the clinical trial based on information provided in accordance with Article 11(3), point (b). If a safety assessing Member State has already been selected for that active substance, the reporting Member State shall inform it about that clinical trial immediately after the authorisation of that clinical trial by at least one Member State concerned in accordance with Article 8 of Regulation (EU) No 536/2014.

6. In the situation described in paragraph 1, point (c), when necessary, the new reporting Member State shall notify the original reporting Member State. The original reporting Member State shall launch and apply the selection procedure for determining the safety assessing Member State in accordance with paragraph 2 without undue delay after the clinical trial in the second Member State has been authorised.

7. When a clinical trial involves the use of several investigational medicinal products with different new active substances for safety cooperation, the reporting Member State shall ensure that a safety assessing Member State is appointed for each new active substance for safety cooperation in that clinical trial.

8. The safety assessing Member State shall be assigned to the active substance and the identity of the safety assessing Member State shall be recorded by the reporting Member State no later than 12 days after the authorisation of a clinical trial involving a new active substance for safety cooperation has been notified in the second Member State.

Article 4

Changing the Safety Assessing Member State

1. When the safety assessing Member State of an active substance is no longer a Member State concerned in any clinical trial involving the use of that active substance, or where a safety assessing Member State has a disproportionate workload in comparison to other Member States, that safety assessing Member State may initiate the procedure for the selection of a new safety assessing Member State in accordance with Article 3(2). That procedure shall, if possible, be launched after the submission by the safety assessing Member State of the final assessment report of the annual safety report.

The safety assessing Member State initiating the procedure referred to in the first subparagraph shall fulfil the tasks assigned to the reporting Member State in Article 3(2).

2. Any Member State can volunteer at any time to take over the role of the safety assessing Member State, provided that the original safety assessing Member State agrees.

3. When a new safety assessing Member State is appointed pursuant to paragraph 1 or 2, the original safety assessing Member State shall record its identity in the information systems referred to in Article 11 for each relevant clinical trial without undue delay.

4. In the situations referred to in paragraphs 1 and 2, the original safety assessing Member State shall continue carrying out its tasks until all final safety assessment reports and records, including the assessment report of the last annual safety report, have been submitted and the new safety assessing Member State has been recorded in the information systems referred to in Article 11 in accordance with paragraph 3.

5. By way of derogation to paragraph 4, the original safety assessing Member State shall be able to resign immediately without finalising the ongoing assessments and without submitting the corresponding assessment reports and records, provided that the new safety assessing Member State agrees.

Article 5

Role and tasks of the safety assessing Member State

1. The safety assessing Member State shall have the following tasks as regards the assigned active substance contained in investigational medicinal products that are used in clinical trials authorised in the Union:

(a) to screen and assess information about all suspected unexpected serious adverse reactions reported in the EudraVigilance database in accordance with Article 42 of Regulation (EU) No 536/2014, regardless of whether they occurred in Member States or in third countries, as well as information contained in annual safety reports, in accordance with Articles 6 and 7 following a risk based approach;

(b) to identify safety concerns in relation to the active substance and the investigational medicinal product, based on the assessments referred to in point (a);

(c) to support, upon request of the reporting Member State, the assessment of aspects related to the reference safety information in the initial application referred to in Articles 5 and 11 of Regulation (EU) No 536/2014 or in an application for substantial modification referred to in Article 16 of that Regulation;

(d) to request missing or further information from sponsors, which is necessary for the assessments or for the cooperation in the safety assessment;

(e) to submit assessment reports and other records related to the safety assessment in accordance with Articles 6, 7 and 11 in order to ensure that all reporting Member States and Member States concerned receive appropriate information on clinical trials using the same active substance;

(f) to prepare and submit recommendations to the reporting Member States and Member States concerned related to the safety of the active substance, so that corrective measures and other actions for safety oversight related to the active substance can be taken if necessary, in accordance with Article 8;

(g) to provide assistance on any additional safety matter related to the particular active substance when requested by the reporting Member States or the Member States concerned.

2. The safety assessing Member State shall carry out its tasks until three months after the end of the last clinical trial with the active substance in all Member States concerned. It shall submit the final assessment report of the last annual safety report for the active substance without undue delay.

3. The responsible ethics committees shall be involved in the safety assessments performed by the safety assessing Member State, when such involvement is provided for in the national law of the safety assessing Member State.

Article 6

Screening and assessment of suspected unexpected serious adverse reactions

1. The screening of the EudraVigilance database referred to in Article 5(1), point (a), shall take place at least once every 15 calendar days.

2. For investigational medicinal products with a marketing authorisation in the Union, the safety assessing Member State may decide to decrease the screening frequency referred to in paragraph 1 to at least once every 30 calendar days.

3. When the state of knowledge about the safety profile of the active substance or the degree of deviation in the use of the active substance from normal clinical practice so requires, the safety assessing Member State shall apply a higher screening frequency than that set out in paragraphs 1 and 2. The safety assessing Member State shall record the outcome and the date of the screening in the information systems referred to in Article 11.

4. In case concerns regarding the safety of the active substance arise from the screening of reported suspected unexpected serious adverse reactions, the safety assessing Member State shall:

(a) assess the information about the suspected unexpected serious adverse reactions and submit an initial assessment as soon as possible but no later than 15 days after the screening;

(b) update the initial assessment as soon as possible after additional information from the sponsor has become available in accordance with Article 42(2) of Regulation (EU) No 536/2014 or in accordance with Article 5(1), point (d), of this Regulation;

(c) notify without undue delay the identified safety concerns in relation to an investigational medicinal product to all reporting Member States and Member States concerned by clinical trials involving the active substance in question.

The submission and sharing of the assessment referred to in points (a) and (b) and the notification referred to in point (c) shall be done through the information systems referred to in Article 11.

5. The safety assessing Member State shall increase the extent and shorten the timelines of the assessment referred to in paragraph 4 if the risk to safety of participants in a clinical trial so requires.

6. If additional information is requested pursuant to Article 5(1), point (d), in the context of the assessment of suspected unexpected serious adverse reactions, and the sponsor does not acknowledge receipt of the request for information by (i) the deadline set by the safety assessing Member State or (ii) 7 days after the request was sent, whichever is the later, the safety assessing Member State shall notify all reporting Member States and Member States concerned by a clinical trial using the active substance to consider taking corrective measures in accordance with Article 77 of Regulation (EU) No 536/2014.

7. Where the safety assessing Member State considers it necessary, based on its assessment(s), it shall submit general recommendations related to the safety of the active substance to the reporting Member States and the Member States concerned enabling them to take corrective measures and other actions for safety oversight related to the active substance.

Article 7

The assessment of the annual safety reports

1. When assessing annual safety reports, the safety assessing Member State shall:

(a) assess the information in all annual safety reports relating to the use of the active substance in clinical trials authorised in the Union, regardless of the pharmaceutical form and strength or indication investigated and regardless of whether the active substance is used in several clinical trials managed by different sponsors;

(b) request additional information pursuant to Article 5(1), point (d), from sponsors and assess their responses. If a sponsor does not provide the information within the deadline set in the request, the safety assessing Member State shall inform relevant reporting Member States and Member States concerned to consider taking corrective measures in accordance with Article 77 of Regulation (EU) No 536/2014;

(c) submit the final assessment report in the information systems referred to in Article 11 within 42 days after the submission of the latest annual safety report or within a maximum of 84 days from the submission of the latest annual safety report if additional information is requested pursuant to point (b);

(d) when necessary, address any safety concerns identified during the assessment, develop recommendations for corrective measures and other actions for safety oversight related to the active substance, and communicate them to the reporting Member States and to the Member States concerned.

2. The safety assessing Member State may increase the extent and shorten the timelines of the assessment referred to in paragraph 1 if the risk to safety of participants in a clinical trial so requires. In this assessment, the safety assessing Member State shall take into account the marketing authorisation status of the investigational medicinal product or active substance, the state of knowledge about the safety profile of the active substance and the degree of deviation in the use of the active substance from normal clinical practice.

3. By way of derogation from paragraph 1, when the sponsor submits a single annual safety report specific to a single clinical trial involving several investigational medicinal products pursuant to Article 43(2) of Regulation (EU) No 536/2014, this annual safety report shall be assessed by the reporting Member State of this particular clinical trial. Upon request of the reporting Member State, the safety assessing Member States for the active substances included in these investigational medicinal products shall support the reporting Member State with this assessment. The reporting Member State shall submit a final assessment report to the information systems referred to in Article 11, and, where necessary, notify safety concerns to the Member States concerned and to every responsible safety assessing Member State for the active substance(s) included in the investigational medicinal products concerned.

Article 8

Recommendations of corrective measures and other actions for safety oversight related to the active substance

1. If the safety assessing Member State identifies safety concerns related to the active substance from sources other than the screening and assessment referred to in Articles 6 and 7, it may submit recommendations for corrective measures and other risk mitigating actions for safety oversight to the reporting Member States and Member States concerned.

2. Following a recommendation pursuant to Article 6(7), Article 7(1), point (d), or paragraph 1 of this Article, the reporting Member States of the clinical trials in which the active substance is used should coordinate the action to be taken for these clinical trials with the Member States concerned.

3. Member States concerned may at any time take corrective measures and other actions for safety oversight related to the active substance in their territory in accordance with Article 77 of Regulation (EU) No 536/2014.

Article 9

The role of the Member States concerned and the reporting Member States in the coordinated safety assessment

1. The reporting Member States and the Member States concerned shall:

(a) support the safety assessing Member State in the coordinated safety assessment and have the possibility to comment and raise queries on the assessments;

(b) take due account of safety concerns in relation to an investigational medicinal product and recommendations by the safety assessing Member State, referred to in Article 8(2), in the context of clinical trial(s) authorised in their territory;

(c) communicate to the safety assessing Member State any relevant safety concerns related to the active substance.

2. The reporting Member State(s):

(a) shall inform existing safety assessing Member States about the authorisation of a new clinical trial involving the same active substance;

(b) shall verify if there is an existing safety assessing Member State for any active substance used in a clinical trial and, if that is not the case, launch and conduct a selection procedure in accordance with Article 3(2). In order to ensure continuity in safety assessment at any time, the reporting Member State shall carry out the tasks of the safety assessing Member State during the selection process;

(c) may request support from the safety assessing Member State for the assessment of changes to the reference safety information when the safety assessing Member State is not a Member State concerned with the clinical trial, in accordance with article 5(1), point (c).

3. Member States shall jointly develop a good practice guidance describing detailed procedures for safety cooperation including corresponding timelines and the content of the assessment reports.

4. Member States may coordinate and facilitate safety surveillance and oversight, related to the active substance, across clinical trials.

Article 10

Lead safety assessing Member State

1. When the safety assessment involves the participation of several safety assessing Member States, they may appoint a lead safety assessing Member State by consensus.

2. The lead safety assessing Member State shall be responsible for the coordination of the safety assessments performed by the safety assessing Member States for an active substance or a pharmacologic class of active substances. Coordinated safety assessment by several safety assessing Member States shall follow the standard screening and assessment timelines as set out in Articles 6 and 7.

CHAPTER III

MISCELLANEOUS PROVISIONS

Article 11

Information systems to support the cooperation in safety assessment

1. The Agency, in its role of manager of the EudraVigilance database, the Clinical Trial Information System and the EU Medicinal Product Dictionary, shall provide the information systems to support the cooperation in safety assessment, covering the functionalities set out in paragraph 3.

2. The Agency, the Commission and the Member States shall evaluate the available information system support on a regular basis, at least annually, and their findings shall be duly considered in the maintenance and updating of the information systems referred to in paragraph 1.

3. The functionalities developed shall:

(a) support searchable listing of active substances contained in investigational medicinal products used in clinical trials that have been authorised in Member States concerned under Regulation (EU) No 536/2014;

(b) enable recording of the safety assessing Member States for a given active substance contained in investigational medicinal products, including retaining the names of previous safety assessing Member States where a new a new safety assessing Member State is appointed for the same active substance;

(c) support searchable listing of different active substances contained in investigational medicinal products used in clinical trials including the identity of the responsible safety assessing Member States for multi-national active substances, or in the case of mono-national active substances, reporting Member States;

(d) enable traceable recording and storage of the assessments of information submitted in reports on suspected unexpected serious adverse reactions and in annual safety reports;

(e) enable all Member States to access annual safety reports, reports on suspected unexpected serious adverse reactions and the assessments referred to in point (d);

(f) enable communication between Member States and between Member States and sponsors;

(g) provide information on when an annual safety report is overdue;

(h) support the screening of suspected unexpected serious adverse reactions, including the provision of predefined reports;

(i) support cooperation between Member States in the assessment of changes to the reference safety information, when required.

4. Clinical trial documentation, which is relevant for the safety assessment, shall be made available to safety assessing Member States, regardless of whether they are a Member State concerned by that clinical trial.

5. The Agency shall, together with the Member States and the Commission, develop the information systems to support the selection and re-selection procedure of the safety assessing Member State, referred to in Articles 3 and 4, by the end of the transition period as laid down in Article 98 of Regulation (EU) No 536/2014.

6. Clinical trials using the same active substance shall be identified in the information systems referred to in paragraph 1, based on the EU active substances code referred to in Article 81(3) of Regulation (EU) No 536/2014.

Article 12

The role of the Clinical Trials Coordination and Advisory Group in coordinated safety assessment

1. The national contact points designated in accordance with Article 83 of Regulation (EU) No 536/2014 shall communicate, within theClinical Trials Coordination and Advisory Group, any concerns related to the functioning of the coordinated safety assessments that they receive from their designating Member States, the safety assessing Member States, or the public.

2. The Clinical Trials Coordination and Advisory Group shall investigate and address concerns related to the functioning of the coordinated safety assessment in due time.

Article 13

Union controls

The Commission may conduct Union controls in accordance with Article 79(1), point (a), of Regulation (EU) No 536/2014, in order to verify whether a Member State correctly supervises compliance with the rules set out for the coordinated safety assessment in Article 44(2) of Regulation (EU) No 536/2014 and in this Regulation.

CHAPTER IV

FINAL PROVISIONS

Article 14

Fees

Member States may levy a fee when they carry out safety assessment activities as a safety assessing Member State and establish reduced fees for non-commercial clinical trials in accordance with Article 86 of Regulation (EU) No 536/2014.

Article 15

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 from 31 January 2022.

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

Done at Brussels, 7 January 2022.

For the Commission
The President
Ursula VON DER LEYEN