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)

CHAPTER VII

SAFETY REPORTING IN THE CONTEXT OF A CLINICAL TRIAL

Article 40

Electronic database for safety reporting

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

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

Article 41

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

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

2 The investigator shall record and document all adverse events, unless the protocol provides differently. The investigator shall report to the sponsor all serious adverse events occurring to subjects treated by him or her in the clinical trial, unless the protocol provides differently.

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

3 The sponsor shall keep detailed records of all adverse events reported to it by the investigator.

4 If the investigator becomes aware of a serious adverse event with a suspected causal relationship to the investigational medicinal product that occurs after the end of the clinical trial in a subject treated by him or her, the investigator shall, without undue delay, report the serious adverse event to the sponsor.

Article 42

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

1 The sponsor of a clinical trial performed in at least one Member State shall report electronically and without delay to the database referred to in Article 40(1) all relevant information about the following suspected unexpected serious adverse reactions.:

a all suspected unexpected serious adverse reactions to investigational medicinal products occurring in that clinical trial, irrespective of whether the suspected unexpected serious adverse reaction has occurred at a clinical trial site in the Union or in a third country;

b all suspected unexpected serious adverse reactions related to the same active substance, regardless of pharmaceutical form and strength or indication investigated, in investigational medicinal products used in the clinical trial, occurring in a clinical trial performed exclusively in a third country, if that clinical trial is sponsored:

(i) by that sponsor, or

(ii) by another sponsor who is either part of the same parent company as the sponsor of the clinical trial, or who develops a medicinal product jointly, on the basis of a formal agreement, with the sponsor of the clinical trial. For this purpose, provision of the investigational medicinal product or information to a future potential marketing authorisation holder on safety matters shall not be considered a joint development; and

c all suspected unexpected serious adverse reactions to investigational medicinal products occurring in any of the subjects of the clinical trial, which are identified by or come to the attention of the sponsor after the end of the clinical trial.

2 The period for the reporting of suspected unexpected serious adverse reactions by the sponsor to the Agency shall take account of the seriousness of the reaction and shall be as follows:

a in the case of fatal or life-threatening suspected unexpected serious adverse reactions, as soon as possible and in any event not later than seven days after the sponsor became aware of the reaction;

b in the case of non-fatal or non-life-threatening suspected unexpected serious adverse reactions, not later than 15 days after the sponsor became aware of the reaction;

c in the case of a suspected unexpected serious adverse reaction which was initially considered to be non-fatal or non-life threatening but which turns out to be fatal or life-threatening, as soon as possible and in any event not later than seven days after the sponsor became aware of the reaction being fatal or life-threatening.

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

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

Article 43

Annual reporting by the sponsor to the Agency

1 Regarding investigational medicinal products other than placebo, the sponsor shall submit annually through the database referred to in Article 40(1) to the Agency a report on the safety of each investigational medicinal product used in a clinical trial for which it is the sponsor.

2 In the case of a clinical trial involving the use of more than one investigational medicinal product, the sponsor may, if provided for in the protocol, submit a single safety report on all investigational medicinal products used in that clinical trial.

3 The annual report referred to in paragraph 1 shall only contain aggregate and anonymised data.

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

Article 44

Assessment by Member States

1 The Agency shall, by electronic means, forward to the Member States concerned the information reported in accordance with Article 42 and 43.

2 Member States shall cooperate in assessing the information reported in accordance with Articles 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.