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COMMISSION IMPLEMENTING REGULATION (EU) No 520/2012

of 19 June 2012

on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council

(Text with EEA relevance)

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CHAPTER I

Pharmacovigilance system master file

Article 1

Structure of the pharmacovigilance system master file

1. The information in the pharmacovigilance system master file shall be accurate and reflect the pharmacovigilance system in place.

2. The marketing authorisation holder may, where appropriate, use separate pharmacovigilance systems for different categories of medicinal products. Each such system shall be described in a separate pharmacovigilance system master file.

All medicinal products for which the marketing authorisation holder obtained a marketing authorisation in accordance with Directive 2001/83/EC or Regulation (EC) No 726/2004 shall be covered by a pharmacovigilance system master file.

Article 2

Content of the pharmacovigilance system master file

The pharmacovigilance system master file shall contain at least all of the following elements:

(1) the following information relating to the qualified person responsible for pharmacovigilance:

(a) a description of the responsibilities demonstrating that the qualified person responsible for pharmacovigilance has sufficient authority over the pharmacovigilance system in order to promote, maintain and improve compliance with pharmacovigilance tasks and responsibilities;

(b) a summary curriculum vitae of the qualified person responsible for pharmacovigilance, including proof of registration with the Eudravigilance database;

(c) contact details of the qualified person responsible for pharmacovigilance;

(d) details of back-up arrangements to apply in the absence of the qualified person responsible for pharmacovigilance;

(e) responsibilities of the contact person for pharmacovigilance issues where such a person has been nominated at national level in accordance with Article 104(4) of Directive 2001/83/EC, including contact details;

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(2) a description of the organisational structure of the marketing authorisation holder, including the list of the site(s) where the following pharmacovigilance activities are undertaken: individual case safety report collection, evaluation, safety database case entry, periodic safety update report production, signal detection and analysis, risk management plan management, pre- and post-authorisation study management, and management of safety variations to the terms of a marketing authorisation;

(3) a description of the location of, functionality of and operational responsibility for computerised systems and databases used to receive, collate, record and report safety information and an assessment of their fitness for purpose;

(4) a description of data handling and recording and of the process used for each of the following pharmacovigilance activities:

(a) the continuous monitoring of the risk-benefit balance of the medicinal product(s), the result of that monitoring and the decision-making process for taking appropriate measures;

(b) operation of the risk management system(s) and of the monitoring of the outcome of risk minimisation measures;

(c) collection, assessment and reporting of individual case safety reports;

(d) drafting and submission of periodic safety update reports;

(e) procedures for communicating safety concerns and safety variations to the summary of product characteristics and package leaflet to healthcare professionals and the general public;

(5) a description of the quality system for the performance of pharmacovigilance activities, including all of the following elements:

(a) a description of the management of human resources referred to in Article 10 containing the following elements: a description of the organisational structure for the performance of pharmacovigilance activities with a reference to the location of qualification records of the personnel; a summary description of the training concept, including a reference to the location of training files; instructions on critical processes;

(b) a description of the record management system referred to in Article 12, including the location of the documents used for pharmacovigilance activities;

(c) a description of the system for monitoring the performance of the pharmacovigilance system and for the compliance with Article 11;

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(6) where applicable, a description of the activities and/or services subcontracted by the marketing authorisation holder in accordance with Article 6(1).

Article 3

Content of the Annex to the pharmacovigilance system master file

The pharmacovigilance system master file shall have an Annex containing the following documents:

(1) a list of medicinal products covered by the pharmacovigilance system master file, including the name of the medicinal product, the international non-proprietary name (INN) of the active substance(s), and the Member State(s) in which the authorisation is valid;

(2) a list of written policies and procedures for the purpose of complying with Article 11(1);

(3) the list of subcontracts referred to in Article 6(2);

(4) a list of the tasks that have been delegated by the qualified person for pharmacovigilance;

(5) a list of all scheduled and completed audits;

(6) where applicable, a list of the performance indicators referred to in Article 9;

(7) where applicable, a list of other pharmacovigilance system master files held by the same marketing authorisation holder;

(8) a logbook containing the information referred to in Article 5(4).

Article 4

Maintenance

1. The marketing authorisation holder shall keep the pharmacovigilance system master file up to date and, where necessary, revise it to take account of experience gained, of technical and scientific progress and of amendments to Directive 2001/83/EC and Regulation (EC) No 726/2004.

2. The pharmacovigilance system master file and its Annex shall be subject to version control and shall indicate the date when it was last updated by the marketing authorisation holder.

3. Any deviations from the pharmacovigilance procedures, their impact and their management shall be documented in the pharmacovigilance system master file until resolved.

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4. Without prejudice to the requirements set out in Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products ([1]), the marketing authorisation holder shall notify immediately the Agency of any change in the location of the pharmacovigilance system master file or changes to the contact details and name of the qualified person responsible for pharmacovigilance. The Agency shall update the Eudravigilance database referred to in Article 24(1) of Regulation (EC) No 726/2004 and, where necessary, the European medicines web-portal referred to in Article 26(1) of Regulation (EC) No 726/2004 accordingly.

Article 5

Form of the documents contained in the pharmacovigilance system master file

1. Pharmacovigilance system master file documents shall be complete and legible. Where appropriate, information may be provided in the form of charts or flow diagrams. All documents shall be indexed and archived so as to ensure their accurate and ready retrieval throughout the period for record-keeping.

2. The particulars and documents of the pharmacovigilance system master file may be presented in modules in accordance with the system delineated in detail in the guidance on good pharmacovigilance practices.

3. The pharmacovigilance system master file may be stored in electronic form provided that the media used for storage remain readable over time and a clearly arranged printed copy can be made available for audits and inspections.

4. The marketing authorisation holder shall record in the logbook referred to in point 8 of Article 3 any alteration of the content of the pharmacovigilance system master file made within the last five years, with the exception of the information referred to in point 1(b) to (e) of Article 2 and in Article 3. The marketing authorisation holder shall indicate in the logbook the date, the person responsible for the alteration and, where appropriate, the reason for the alteration.

Article 6

Subcontracting

1. The marketing authorisation holder may subcontract certain activities of the pharmacovigilance system to third parties. It shall nevertheless retain full responsibility for the completeness and accuracy of the pharmacovigilance system master file.

2. The marketing authorisation holder shall draw up a list of its existing subcontracts between it and the third parties referred to in paragraph 1, specifying the product(s) and territory(ies) concerned.

([1]) OJ L 334, 24.11.2008, p. 7.

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Article 7

Availability and location of the pharmacovigilance system master file

1. The pharmacovigilance system master file shall be located either at the site in the Union where the main pharmacovigilance activities of the marketing authorisation holder are performed or at the site in the Union where the qualified person responsible for pharmacovigilance operates.

2. The marketing authorisation holder shall ensure that the qualified person for pharmacovigilance has permanent access to the pharmacovigilance system master file.

3. The pharmacovigilance system master file shall be permanently and immediately available for inspection at the site where it is kept.

Where the pharmacovigilance system master file is kept in electronic form in accordance with Article 5(3), it is sufficient for the purposes of this Article that the data stored in electronic form is directly available at the site where the pharmacovigilance system master file is kept.

4. For the purposes of Article 23(4) of Directive 2001/83/EC, the national competent authority may limit its request to specific parts or modules of the pharmacovigilance system master file and the marketing authorisation holder shall bear the costs of submitting the copy of the pharmacovigilance system master file.

5. The national competent authority and the Agency may request the marketing authorisation holder to submit a copy of the logbook referred to in point 8 of Article 3 at regular intervals.

CHAPTER II

Minimum requirements for the quality systems for the performance of pharmacovigilance activities

Section 1

General provisions

Article 8

Quality system

1. Marketing authorisation holders, the national competent authorities and the Agency shall establish and use a quality system that is adequate and effective for the performance of their pharmacovigilance activities.

2. The quality system shall cover organisational structure, responsibilities, procedures, processes and resources, appropriate resource management, compliance management and record management.

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3. The quality system shall be based on all of the following activities:

(a) quality planning: establishing structures and planning integrated and consistent processes;

(b) quality adherence: carrying out tasks and responsibilities in accordance with quality requirements;

(c) quality control and assurance: monitoring and evaluating how effectively the structures and processes have been established and how effectively the processes are being carried out;

(d) quality improvements: correcting and improving the structures and processes where necessary.

4. All elements, requirements and provisions adopted for the quality system shall be documented in a systematic and orderly manner in the form of written policies and procedures, such as quality plans, quality manuals and quality records.

5. All persons involved in the procedures and processes of the quality systems established by the national competent authorities and the Agency for the performance of pharmacovigilance activities shall be responsible for the good functioning of those quality systems and shall ensure a systematic approach towards quality and towards the implementation and maintenance of the quality system.

Article 9

Performance indicators

1. The marketing authorisation holder, national competent authorities and the Agency may use performance indicators to continuously monitor the good performance of pharmacovigilance activities.

2. The Agency may publish a list of performance indicators on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee.

Section 2

Minimum requirements for the quality systems for the performance of pharmacovigilance activities by marketing authorisation holders

Article 10

Management of human resources

1. The marketing authorisation holder shall have sufficient competent and appropriately qualified and trained personnel available for the performance of pharmacovigilance activities.

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For the purposes of the first subparagraph, the market authorisation holder shall ensure that the qualified person responsible for pharmacovigilance has acquired adequate theoretical and practical knowledge for the performance of pharmacovigilance activities. Where the qualified person has not completed basic medical training in accordance with Article 24 of Directive 2005/36/EC of the European Parliament and of the Council of 7 September 2005 on the recognition of professional qualifications ([1]), the market authorisation holder shall ensure that the qualified person responsible for pharmacovigilance is assisted by a medically trained person. This assistance shall be duly documented.

2. The duties of the managerial and supervisory staff, including the qualified person responsible for pharmacovigilance, shall be defined in job descriptions. Their hierarchical relationships shall be defined in an organisational chart. The marketing authorisation holder shall ensure that the qualified person responsible for pharmacovigilance has sufficient authority to influence the performance of the quality system and the pharmacovigilance activities of the marketing authorisation holder.

3. All personnel involved in the performance of pharmacovigilance activities shall receive initial and continued training in relation to their role and responsibilities. The marketing authorisation holder shall keep training plans and records for documenting, maintaining and developing the competences of personnel and make them available for audit or inspection.

4. The marketing authorisation holder shall provide appropriate instructions on the processes to be used in case of urgency, including business continuity.

Article 11

Compliance management

1. Specific quality system procedures and processes shall be in place in order to ensure the following:

(a) the continuous monitoring of pharmacovigilance data, the examination of options for risk minimisation and prevention and appropriate measures are taken by the marketing authorisation holder;

(b) the scientific evaluation by the marketing authorisation holder of all information on the risks of medicinal products, as referred to in the second subparagraph of Article 101(1) of Directive 2001/83/EC;

(c) the submission of accurate and verifiable data on serious and non-serious adverse reactions to the Eudravigilance database within the time limits provided for in the first and second subparagraphs respectively of Article 107(3) of Directive 2001/83/EC;

(d) the quality, integrity and completeness of the information submitted on the risks of medicinal products, including processes to avoid duplicate submissions and to validate signals in accordance with Article 21(2);

([1]) OJ L 255, 30.9.2005, p. 22.

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(e) effective communication by the marketing authorisation holder with the national competent authorities and the Agency, including communication on new risks or changed risks, the pharmacovigilance system master file, risk management systems, risk minimisation measures, periodic safety update reports, corrective and preventive actions, and post-authorisation studies;

(f) the update of product information by the marketing authorisation holder in the light of scientific knowledge, including the assessments and recommendations made public via the European medicines web-portal, and on the basis of a continuous monitoring by the marketing authorisation holder of information published on the European medicines web-portal;

(g) appropriate communication by the marketing authorisation holder of relevant safety information to healthcare professionals and patients.

2. Where a marketing authorisation holder has subcontracted some of its pharmacovigilance tasks, it shall retain responsibility for ensuring that an effective quality system is applied in relation to those tasks.

Article 12

Record management and data retention

1. Marketing authorisation holders shall record all pharmacovigilance information and ensure that it is handled and stored so as to allow for accurate reporting, interpretation and verification of that information.

Marketing authorisation holders shall put in place a record management system for all documents used for pharmacovigilance activities that ensures the retrievability of those documents as well as the traceability of the measures taken to investigate safety concerns, of the timelines for those investigations and of decisions on safety concerns, including their date and the decision-making process.

Marketing authorisation holders shall establish mechanisms enabling the traceability and follow-up of adverse reaction reports.

2. Marketing authorisation holders shall arrange for the elements referred to in Article 2 to be kept for at least five years after the system as described in the pharmacovigilance system master file has been formally terminated by the marketing authorisation holder.

Pharmacovigilance data and documents relating to individual authorised medicinal products shall be retained as long as the product is authorised and for at least 10 years after the marketing authorisation has ceased to exist. However, the documents shall be retained for a longer period where Union law or national law so requires.

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Article 13

Audit

1. Risk-based audits of the quality system shall be performed at regular intervals to ensure that the quality system complies with the quality system requirements set out in Articles 8, 10, 11 and 12 and to determine its effectiveness. Those audits shall be conducted by individuals who have no direct involvement in or responsibility for the matters or processes being audited.

2. Corrective action(s), including a follow-up audit of deficiencies, shall be taken where necessary. A report on the results of the audit shall be drawn up for each audit and follow-up audit. The audit report shall be sent to the management responsible for the matters audited. The dates and results of audits and follow-up audits shall be documented in accordance with the second subparagraph of Article 104(2) of Directive 2001/83/EC.

Section 3

Minimum requirements for the quality systems for the performance of pharmacovigilance activities by national competent authorities and the Agency

Article 14

Management of human resources

1. The national competent authorities and the Agency shall have sufficient competent and appropriately qualified and trained personnel available for the performance of pharmacovigilance activities.

The organisational structures and the distribution of tasks and responsibilities shall be clear and, to the extent necessary, accessible. Contact points shall be established.

2. All personnel involved in the performance of pharmacovigilance activities shall receive initial and continued training. The national competent authorities and the Agency shall keep training plans and records for documenting, maintaining and developing the competences of personnel and shall make them available for audit.

3. Appropriate instructions on the processes to be used in case of urgency, including business continuity, shall be provided by the national competent authorities and by the Agency to their personnel.

Article 15

Compliance management

1. The national competent authorities and the Agency shall establish specific procedures and processes in order to achieve all of the following objectives:

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(a) ensuring the evaluation of the quality, including completeness, of pharmacovigilance data submitted;

(b) ensuring the assessment of pharmacovigilance data and its processing within the timelines provided by Directive 2001/83/EC and Regulation (EC) No 726/2004;

(c) ensuring independence in the performance of pharmacovigilance activities;

(d) ensuring effective communication among national competent authorities and between the national competent authorities and the Agency as well as with patients, healthcare professionals, marketing authorisation holders and the general public;

(e) guaranteeing that the national competent authorities and the Agency inform each other and the Commission of their intention to make announcements relating to the safety of a medicinal product authorised in several Member States or an active substance contained in such a medicinal product in accordance with Article 106a of Directive 2001/83/EC;

(f) conducting inspections, including pre-authorisation inspections.

2. In addition to the procedures referred to in paragraph 1, national competent authorities shall establish procedures for collecting and recording all suspected adverse reactions that occur in their territory.

3. The Agency shall establish procedures for the monitoring of medical literature in accordance with Article 27 of Regulation (EC) No 726/2004.

Article 16

Record management and data retention

1. The national competent authorities and the Agency shall record all pharmacovigilance information and ensure that it is handled and stored so as to allow for accurate reporting, interpretation and verification of that information.

They shall put in place a record management system for all documents used for pharmacovigilance activities that ensures the retrievability of those documents as well as the traceability of the measures taken to investigate safety concerns, of the timelines for those investigations and of decisions on safety concerns, including their date and the decision-making process.

2. The national competent authorities and the Agency shall arrange for the essential documents describing their pharmacovigilance system to be kept for at least five years after the system has been formally terminated.

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Pharmacovigilance data and documents relating to individual authorised medicinal products shall be retained as long as the product is authorised and for at least 10 years after the marketing authorisation has expired. However, the documents shall be retained for a longer period where Union law or national law so requires.

Article 17

Audit

1. Risk-based audits of the quality system shall be performed at regular intervals according to a common methodology to ensure that the quality system complies with the requirements set out in Articles 8, 14, 15 and 16 and to ensure its effectiveness.

2. Corrective action, including a follow-up audit of deficiencies, shall be taken where necessary. The audit report shall be sent to the management responsible for the matters audited. The dates and results of audits and follow-up audits shall be documented.

CHAPTER III

Minimum requirements for the monitoring of data in the Eudravigilance database

Article 18

General requirements

1. The Agency and national competent authorities shall cooperate in the monitoring of the data available in the Eudravigilance database.

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2. Marketing authorisation holders shall monitor the data available in the Eudravigilance database and use it together with data from other available sources.

3. National competent authorities and the Agency shall ensure the continuous monitoring of the Eudravigilance database with a frequency proportionate to the identified risks, the potential risks and the need for additional information.

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4. The competent authority of each Member State shall be responsible for monitoring the data originating in the territory of that Member State.

Article 19

Identification of changed risks and new risks

1. The identification of new risks or changed risks shall be based on the detection and analysis of the signals concerning a medicinal product or an active substance.

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For the purposes of this chapter, ‘signal’ means information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, which is judged to be of sufficient likelihood to justify verificatory action.

For the purpose of monitoring data in the Eudravigilance database, only signals related to an adverse reaction shall be considered.

2. The detection of a signal shall be based on a multidisciplinary approach. Signal detection within the Eudravigilance database shall be complemented by statistical analysis, where appropriate. After consultation with the Pharmacovigilance Risk Assessment Committee, the Agency may publish a list of medical events that have to be taken into account for the detection of a signal.

Article 20

Methodology for determining the evidentiary value of a signal

1. National competent authorities, marketing authorisation holders and the Agency shall determine the evidentiary value of a signal by using a recognised methodology taking into account the clinical relevance, quantitative strength of the association, the consistency of the data, the exposure–response relationship, the biological plausibility, experimental findings, possible analogies and the nature and quality of the data.

2. Different types of factors may be taken into account for the prioritisation of signals, in particular whether the association or medicinal product is new, factors related to the strength of the association, factors related to the seriousness of the reaction involved and factors related to the documentation of reports to the Eudravigilance database.

3. The Pharmacovigilance Risk Assessment Committee shall regularly review the methodology(ies) used and publish recommendations, as appropriate.

Article 21

Signal management process

1. The signal management process shall include the following activities: signal detection, signal validation, signal confirmation, signal analysis and prioritisation, signal assessment, and recommendation for action.

For the purposes of this Article, ‘signal validation’ means the process of evaluating the data supporting the detected signal in order to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore justifies further analysis of the signal.

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3. Where it is considered that a validated signal requires further analysis, it shall be confirmed as soon as possible and no later than 30 days from its receipt as follows:

(a) where the signal concerns a product authorised in accordance with Directive 2001/83/EC, it shall be confirmed by the competent authority of a Member State in which the medicinal product is marketed or of any lead Member State or co-leader appointed in accordance with Article 22(1);

(b) where the signal concerns a product authorised in accordance with Regulation (EC) No 726/2004, it shall be confirmed by the Agency in collaboration with the Member States.

When analysing the validated signal, national competent authorities and the Agency may take into account other information available on the medicinal product.

Where the validity of the signal is not confirmed, special attention shall be paid to non-confirmed signals concerning a medicinal product where those signals are subsequently followed by new signals concerning the same medicinal product.

4. Without prejudice to paragraphs 2 and 3, national competent authorities and the Agency shall validate and confirm any signal that they have detected during their continuous monitoring of the Eudravigilance database.

5. Any confirmed signal shall be entered in the tracking system administered by the Agency and shall be transmitted to the Pharmacovigilance Risk Assessment Committee for the initial analysis and prioritisation of signals in accordance with Article 107h(2) of Directive 2001/83/EC and Article 28a(2) of Regulation (EC) No 726/2004.

6. The Agency shall inform forthwith the marketing authorisation holder(s) concerned of the conclusions of the Pharmacovigilance Risk Assessment Committee of the assessment of any confirmed signal.

Article 22

Worksharing for signal management

1. For medicinal products authorised in accordance with Directive 2001/83/EC in more than one Member State and for active substances contained in several medicinal products where at least one marketing authorisation has been granted in accordance with Directive 2001/83/EC, Member States may agree within the coordination group provided for by Article 27 of Directive 2001/83/EC to appoint a lead Member State and, where appropriate, a co-leader. Any such appointment shall be reviewed at least every four years.

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The lead Member State shall monitor the Eudravigilance database and shall validate and confirm signals in accordance with Article 21(3) and (4) on behalf of the other Member States. The Member State appointed as co-leader shall assist the lead Member State in the fulfilment of its tasks.

2. When appointing a lead Member State and as appropriate a co-leader, the coordination group may take into account whether any Member State is acting as reference Member State in accordance with Article 28(1) of Directive 2001/83/EC or as a rapporteur for the assessment of periodic safety update reports in accordance with Article 107e of that Directive.

3. The Agency shall publish on the European medicines web-portal a list of the active substances that are subject to worksharing in accordance with this Article and the lead Member State and co-leader appointed for monitoring those substances in the Eudravigilance database.

4. Without prejudice to paragraph 1, all Member States shall remain responsible for monitoring the data in the Eudravigilance database in accordance with Article 107h(1)(c) and Article 107h(3) of Directive 2001/83/EC.

5. For medicinal products authorised in accordance with Regulation (EC) No 726/2004, the Agency shall be assisted in the monitoring of data in the Eudravigilance database by the rapporteur appointed by the Pharmacovigilance Risk Assessment Committee in accordance with Article 62(1) of Regulation (EC) No 726/2004.

Article 23

Signal detection support

The Agency shall support the monitoring of the Eudravigilance database by providing national competent authorities with access to the following information:

(a) data outputs and statistical reports allowing a review of all adverse reactions reported to the Eudravigilance database in relation to an active substance or a medicinal product;

(b) customised queries supporting the evaluation of individual case safety reports and case series;

(c) customised grouping and stratification of data enabling the identification of patient groups with a higher risk of occurrence of adverse reactions or with a risk of a more severe adverse reaction;

(d) statistical signal detection methods.

The Agency shall also ensure appropriate support for the monitoring of the Eudravigilance database by marketing authorisation holders.

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Article 24

Signal detection audit trail

1. The national competent authorities and the Agency shall keep an audit trail of their signal detection activities conducted in the Eudravigilance database and of the relevant queries and their results.

2. The audit trail shall allow traceability of how signals have been detected and of how validated and confirmed signals have been assessed.

CHAPTER IV

Use of terminology, formats and standards

Article 25

Use of internationally agreed terminology

1. For the classification, retrieval, presentation, risk-benefit evaluation and assessment, electronic exchange and communication of pharmacovigilance and medicinal product information, Member States, marketing authorisation holders and the Agency shall apply the following terminology:

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

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

(c) the terminology set out in EN ISO 11615:2012, Health Informatics, Identification of Medicinal Products (IDMP) standard, ‘Data elements and structures for unique identification and exchange of regulated medicinal product information’ (ISO/FDIS 11615:2012);

(d) the terminology set out in EN ISO 11616:2012 Health Informatics, Identification of Medicinal Products (IDMP) standard, ‘Data elements and structures for unique identification and exchange of regulated pharmaceutical product information’ (ISO/FDIS 11616:2012);

(e) the terminology set out in EN ISO 11238:2012 Health Informatics, Identification of Medicinal Products (IDMP) standard, ‘Data elements and structures for unique identification and exchange of regulated information on substances’ (ISO/FDIS 11238:2012);

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(f) the terminology set out in EN ISO 11239:2012 Health Informatics, Identification of Medicinal Products (IDMP) standard, ‘Data elements and structures for unique identification and exchange of regulated information on pharmaceutical dose forms, units of presentation and routes of administration’ (ISO/FDIS 11239:2012);

(g) the terminology set out in EN ISO 11240:2012 Health Informatics, Identification of Medicinal Products (IDMP) standard, ‘Data elements and structures for unique identification and exchange of units of measurement’ (ISO/FDIS 11240:2012).

2. Member States, national competent authorities or marketing authorisation holders shall request the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, the European Pharmacopoeia Commission, the European Committee for Standardisation or the International Organisation for Standardisation to add a new term to the terminology referred to in paragraph 1, where necessary. In such a case, they shall inform the Agency accordingly.

3. Member States, marketing authorisation holders and the Agency shall monitor the use of the terminology referred to in paragraph 1 either systematically or by regular random evaluation.

Article 26

Use of internationally agreed formats and standards

1. For the description, retrieval, presentation, risk-benefit evaluation and assessment, electronic exchange and communication of pharmacovigilance and medicinal product information, national competent authorities, marketing authorisation holders and the Agency shall apply the following formats and standards:

(a) the Extended Eudravigilance Medicinal Product Report Message (XEVPRM), which is the format for the electronic submission of information on all medicinal products for human use authorised in the Union in accordance with the second subparagraph of Article 57(2) of Regulation (EC) No 726/2004, as published by the Agency;

(b) ICH E2B(R2) ‘Maintenance of the ICH guideline on clinical safety data management: data elements for transmission of Individual Case Safety Reports’;

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(c) ICH M2 standard ‘Electronic Transmission of Individual Case Safety Reports Message Specification’.

2. For the purpose of paragraph 1 national competent authorities, marketing authorisation holders and the Agency may also apply the following formats and standards:

(a) EN ISO 27953-2:2011 Health Informatics, Individual case safety reports (ICSRs) in pharmacovigilance — Part 2: Human pharmaceutical reporting requirements for ICSR (ISO 27953-2:2011);

(b) EN ISO 11615:2012, Health Informatics, Identification of Medicinal Products (IDMP) standard, ‘Data elements and structures for unique identification and exchange of regulated medicinal product information’ (ISO/FDIS 11615:2012);

(c) EN ISO 11616:2012, Health Informatics, Identification of Medicinal Products (IDMP) standard ‘Data elements and structures for unique identification and exchange of regulated pharmaceutical product information’ (ISO/FDIS 11616:2012);

(d) EN ISO 11238:2012, Health Informatics, Identification of Medicinal Products (IDMP) standard, ‘Data elements and structures for unique identification and exchange of regulated information on substances’ (ISO/FDIS 11238:2012);

(e) EN ISO 11239:2012, Health Informatics, Identification of Medicinal Products (IDMP) standard, ‘Data elements and structures for unique identification and exchange of regulated information on pharmaceutical dose forms, units of presentation and routes of administration’ (ISO/FDIS 11239:2012);

(f) EN ISO 11240:2012, Health Informatics, Identification of Medicinal Products (IDMP) standard, ‘Data elements and structures for unique identification and exchange of units of measurement’ (ISO/FDIS 11240:2012).

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CHAPTER V

Transmission of reports of suspected adverse reactions

Article 27

Individual case safety reports

Individual case safety reports shall be used for reporting to the Eudravigilance database suspected adverse reactions to a medicinal product that occur in a single patient at a specific point in time.

Article 28

Content of the individual case safety report

1. Member States and marketing authorisation holders shall ensure that individual case safety reports are as complete as possible and shall communicate the updates of those reports to the Eudravigilance database in an accurate and reliable manner.

In the case of expedited reporting, the individual case safety report shall include at least an identifiable reporter, an identifiable patient, one suspected adverse reaction and the medicinal product(s) concerned.

2. Member States and marketing authorisation holders shall record the details necessary for obtaining follow-up information on individual case safety reports. The follow-up of reports shall be adequately documented.

3. When reporting suspected adverse reactions, Member States and marketing authorisation holders shall provide all available information on each individual case, including the following:

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

(b) literature reference in accordance with the ‘Vancouver style’ as developed by the International Committee of Medical Journal Editors ([1]) for adverse reactions reported in the worldwide literature, including a comprehensive English summary of the article;

([1]) International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. N Engl J Med 1997; 336:309-15.

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(c) study type, study name and the sponsor's study number or study registration number for reports from studies not covered by Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 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 ([1]);

(d) information on the primary source(s): information identifying the reporter, including Member State of residence and professional qualifications;

(e) information identifying the patient (and parent in the case of a parent-child report), including age at the time of the onset of the first reaction, age group, gestation period when reaction/event was observed in the foetus, weight, height or gender, last menstrual date and/or gestation period at time of exposure;

(f) relevant medical history and concurrent conditions;

(g) the name, as defined in Article 1(20) of Directive 2001/83/EC, of the medicinal product(s) suspected to be related to the occurrence of the adverse reaction, including interacting medicinal products or, where the name is not known, the active substance(s) and any other characteristics that allow for the identification of the medicinal product(s), including the name of the marketing authorisation holder, marketing authorisation number, country of marketing authorisation, pharmaceutical form and (parent) route(s) of administration, indication(s) for use in the case, dose administered, start date and end date of administration, actions taken with the medicinal product(s), effect of the dechallenge and rechallenge for suspect medicinal products;

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

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

(j) information on the suspected adverse reaction(s): start date and end date of the suspected adverse reaction(s) or duration, seriousness, outcome of the suspected adverse reaction(s) at the time of last observation, time intervals between suspect medicinal product administration and start of adverse reaction, the original reporter's words or short phrases used to describe the reaction(s) and Member State or third-country of occurrence of the suspected adverse reaction;

([1]) OJ L 121, 1.5.2001, p. 34.

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

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

(m) a case narrative, where possible, providing all relevant information for individual cases with the exception of non-serious adverse reactions;

(n) reasons for nullifying or amending an individual case safety report.

For the purposes of point (b), upon request of the Agency, the marketing authorisation holder that transmitted the initial report shall provide a copy of the relevant article taking into account copyright restrictions, and a full translation of that article into English.

For the purposes of point (h), a follow-up procedure shall be in place to obtain the batch number where it is not indicated in the initial report.

For the purposes of point (m), the information shall be presented in a logical time sequence, in the chronology of the patient's experience including clinical course, therapeutic measures, outcome and follow-up information obtained; any relevant autopsy or post-mortem findings shall also be summarised in the narrative.

4. Where suspected adverse reactions are reported in narrative and textual descriptions in an official language of the Union other than English, the original verbatim text and a summary thereof in English shall be provided by the marketing authorisation holder.

Member States may report case narratives in their official language(s). For those reports, case translations shall be provided where requested by the Agency or other Member States for the evaluation of potential signals.

English shall be used for the reporting of suspected adverse reactions originating outside the Union.

Article 29

Format of electronic transmission of suspected adverse reactions

Member States and marketing authorisation holders shall use the formats provided for in Article 26 and the terminology provided for in Article 25 for the electronic transmission of suspected adverse reactions.

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CHAPTER VI

Risk management plans

Article 30

Content of the risk management plan

1. The risk management plan established by the marketing authorisation holder shall contain the following elements:

(a) an identification or characterisation of the safety profile of the medicinal product(s) concerned;

(b) an indication of how to characterise further the safety profile of the medicinal product(s) concerned;

(c) a documentation of measures to prevent or minimise the risks associated with the medicinal product, including an assessment of the effectiveness of those interventions;

(d) a documentation of post-authorisation obligations that have been imposed as a condition of the marketing authorisation.

2. Products containing the same active substance and belonging to the same marketing authorisation holder may be subject, where appropriate, to the same risk management plan.

3. Where a risk management plan refers to post-authorisation studies, it shall indicate whether those studies are initiated, managed or financed by the marketing authorisation holder voluntarily or pursuant to obligations imposed by the national competent authorities, the Agency or the Commission. All post-authorisation obligations shall be listed in the summary of the risk management plan together with a timeframe.

Article 31

Summary of the risk management plan

1. The summary of the risk management plan to be made publicly available in accordance with point (c) of Article 106 of Directive 2001/83/EC and Article 26(1)(c) of Regulation (EC) No 726/2004 shall include key elements of the risk management plan with a specific focus on risk minimisation activities and, with regard to the safety specification of the medicinal product concerned, important information on potential and identified risks as well as missing information.

2. Where a risk management plan concerns more than one medicinal product, a separate summary of the risk management plan shall be provided for each medicinal product.

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Article 32

Updates of the risk management plan

1. Where the marketing authorisation holder updates a risk management plan, it shall submit the updated risk management plan to the national competent authorities or the Agency as appropriate. After agreement with the national competent authorities or the Agency as appropriate, the marketing authorisation holder may submit only the modules concerned by the update. If necessary, the marketing authorisation holder shall provide the competent authorities or the Agency with an updated summary of the risk management plan.

2. Each submission of the risk management plan shall have a distinct version number and shall be dated.

Article 33

Format of the risk management plan

The risk management plan shall be in the format set out in Annex I.

CHAPTER VII

Periodic safety update reports

Article 34

Content of periodic safety update reports

1. The periodic safety update report shall be based on all available data and shall focus on new information which has emerged since the data lock point of the last periodic safety update report.

2. The periodic safety update report shall provide an accurate estimate of the population exposed to the medicinal product, including all data relating to the volume of sales and volume of prescriptions. This estimate of exposure shall be accompanied by a qualitative and quantitative analysis of actual use, which shall indicate, where appropriate, how actual use differs from the indicated use based on all data available to the marketing authorisation holder, including the results of observational or drug utilisation studies.

3. The periodic safety update report shall contain the results of assessments of the effectiveness of risk minimisation activities relevant to the risk–benefit assessment.

4. Marketing authorisation holders shall not be required to include systematically detailed listings of individual cases, including case narratives, in the periodic safety update report. However, they shall provide case narratives in the relevant risk evaluation section of the periodic safety update report where integral to the scientific analysis of a signal or safety concern in the relevant risk evaluation section.

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5. Based on the evaluation of the cumulative safety data and the risk-benefit analysis, the marketing authorisation holder shall draw conclusions in the periodic safety update report as to the need for changes and/or actions, including implications for the approved summary of product characteristics for the product(s) for which the periodic safety update report is submitted.

6. Unless otherwise specified in the list of Union reference dates and frequency of submission referred to in Article 107c of Directive 2001/83/EC or agreed with the national competent authorities or the Agency, as appropriate, a single periodic safety update report shall be prepared for all medicinal products containing the same active substance and authorised for one marketing authorisation holder. The periodic safety update report shall cover all indications, routes of administration, dosage forms and dosing regimens, irrespective of whether authorised under different names and through separate procedures. Where relevant, data relating to a particular indication, dosage form, route of administration or dosing regimen shall be presented in a separate section of the periodic safety update report and any safety concerns shall be addressed accordingly.

7. Unless otherwise specified in the list of Union reference dates and frequency of submission referred to in Article 107c of Directive 2001/83/EC, if the substance that is the subject of the periodic safety update report is also authorised as a component of a fixed combination medicinal product, the marketing authorisation holder shall either submit a separate periodic safety update report for the combination of active substances authorised for the same marketing authorisation holder, with cross-references to the single-substance periodic safety update report(s), or provide the combination data within one of the single-substance periodic safety update reports.

Article 35

Format of periodic safety update reports

1. Electronic periodic safety update reports shall be submitted in the format set out in Annex II.

2. The Agency may publish templates for the modules set out in Annex II.

CHAPTER VIII

Post-authorisation safety studies

Article 36

Scope

1. This chapter applies to non-interventional post-authorisation safety studies initiated, managed or financed by a marketing authorisation holder under obligations imposed by a national competent authority, the Agency or the Commission in accordance with Articles 21a and 22a of Directive 2001/83/EC and Articles 10 and 10a of Regulation (EC) No 726/2004.

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2. The marketing authorisation holder shall submit the study protocol, the abstract of the final study report and the final study report which have been provided in accordance with Articles 107n and 107p of Directive 2001/83/EC in English except for studies to be conducted in only one Member State that requests the study according to Article 22a of Directive 2001/83/EC. For the latter studies the marketing authorisation holder shall provide an English translation of the title and abstract of the study protocol as well as an English translation of the abstract of the final study report.

3. The marketing authorisation holder shall ensure that all study information is handled and stored so as to allow for accurate reporting, interpretation and verification of that information and shall ensure that the confidentiality of the records of the study subjects remains protected. The marketing authorisation holder shall ensure that the analytical dataset and statistical programmes used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection.

4. The Agency may publish appropriate templates for the protocol, abstract and final study report.

Article 37

Definitions

For the purposes of this chapter, the following definitions shall apply:

(1) ‘Start of data collection’ means the date from which information on the first study subject is first recorded in the study dataset or, in the case of the secondary use of data, the date from which data extraction starts;

(2) ‘End of data collection’ means the date from which the analytical dataset is completely available.

Article 38

Format of post-authorisation safety studies

Protocols, abstracts and final study reports for non-interventional post-authorisation safety studies shall be submitted in the format set out in Annex III.

CHAPTER IX

Final provisions

Article 39

Data protection

This Regulation shall apply without prejudice to the obligations of national competent authorities and marketing authorisation holders relating to their processing of personal data under Directive 95/46/EC or the obligations of the Agency relating to its processing of personal data under Regulation (EC) No 45/2001.

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Article 40

Transitional provisions

1. The obligation on the part of marketing authorisation holders, national competent authorities and the Agency to use the terminology provided for in points (c) to (g) of Article 25 shall apply from 1 July 2016.

2. Article 26(2) shall apply from 1 July 2016.

3. The obligation on the part of the marketing authorisation holder to comply with the format and content as provided for in Articles 29 to 38 shall apply from 10 January 2013.

Article 41

Entry into force and application

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 10 July 2012.

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

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ANNEX I

Risk management plans

Format of the risk management plan

The risk management plan shall consist of the following modules:

Part I: Product(s) overview

Part II: Safety specification

- Module SI: Epidemiology of the indication(s) and target population(s)
- Module SII: Non-clinical part of the safety specification
- Module SIII: Clinical trial exposure
- Module SIV: Populations not studied in clinical trials
- Module SV: Post-authorisation experience
- Module SVI: Additional EU requirements for the safety specification
- Module SVII: Identified and potential risks
- Module SVIII: Summary of the safety concerns

Part III: Pharmacovigilance plan (including post-authorisation safety studies)

Part IV: Plans for post-authorisation efficacy studies

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Part VI: Summary of the risk management plan

Part VII: Annexes

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ANNEX II

Format of the electronic periodic safety update reports

The periodic safety update report shall consist of the following modules:

Part I Title page including signature

Part II Executive Summary

Part III Table of contents

1. Introduction

2. Worldwide marketing authorisation status

3. Actions taken in the reporting interval for safety reasons

4. Changes to reference safety information

5. Estimated exposure and use patterns

   5.1. Cumulative subject exposure in clinical trials

   5.2. Cumulative and interval patient exposure from marketing experience

6. Data in summary tabulations

   6.1. Reference information

   6.2. Cumulative summary tabulations of serious adverse events from clinical trials

   6.3. Cumulative and interval summary tabulations from post-marketing data sources

7. Summaries of significant findings from clinical trials during the reporting interval

   7.1. Completed clinical trials

   7.2. Ongoing clinical trials

   7.3. Long-term follow-up

   7.4. Other therapeutic use of medicinal product

   7.5. New safety data related to fixed combination therapies

8. Findings from non-interventional studies

9. Information from other clinical trials and sources

10. Non-clinical data

11. Literature

12. Other periodic reports

13. Lack of efficacy in controlled clinical trials

14. Late-breaking information

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15. Overview on signals: New, ongoing or closed

16. Signal and risk evaluation

    16.1. Summaries of safety concerns

    16.2. Signal evaluation

    16.3. Evaluation of risks and new information

    16.4. Characterisation of risks

    16.5. Effectiveness of risk minimisation (if applicable)

17. Benefit evaluation

    17.1. Important baseline efficacy and effectiveness information

    17.2. Newly identified information on efficacy and effectiveness

    17.3. Characterisation of benefits

18. Integrated benefit-risk analysis for authorised indications

    18.1. Benefit-risk context — Medical need and important alternatives

    18.2. Benefit-risk analysis evaluation

19. Conclusions and actions

20. Appendices to the periodic safety update report

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ANNEX III

Protocols, abstracts and final study reports for post-authorisation safety studies

1. *Format of the study protocol*

1. Title: informative title including a commonly used term indicating the study design and the medicinal product, substance or drug class concerned, and a sub-title with a version identifier and the date of the last version.

2. Marketing authorisation holder.

3. Responsible parties including a list of all collaborating institutions and other relevant study sites.

4. Abstract: stand-alone summary of the study protocol, including the following subsections:

   (a) title with subtitles including version and date of the protocol and name and affiliation of the main author;

   (b) rationale and background;

   (c) research question and objectives;

   (d) study design;

   (e) population;

   (f) variables;

   (g) data sources;

   (h) study size;

   (i) data analysis;

   (j) milestones.

5. Amendments and updates: any substantial amendment and update to the study protocol after the start of data collection, including a justification for the amendment or update, the date of the change, and a reference to the section of the protocol where the change has been made.

6. Milestones: table with planned dates for the following milestones:

   (a) start of data collection;

   (b) end of data collection;

   (c) study progress report(s) as referred to in Article 107m(5) of Directive 2001/83/EC;

   (d) interim report(s) of study results, if applicable;

   (e) final report of study results.

7. Rationale and background: description of the safety hazard(s), the safety profile or the risk management measures that led to the study being imposed as an obligation for a marketing authorisation.

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8. Research question and objectives in accordance with the decision of the national competent authority that imposed the study as an obligation.

9. Research methods: description of the research methods, including:

   (a) study design;

   (b) setting: study population defined in terms of persons, place, time period, and selection criteria, including the rationale for any inclusion and exclusion criteria. Where any sampling from a source population is undertaken, a description of the source population and details of sampling methods shall be provided. Where the study design is a systematic review or a meta-analysis, the criteria for the selection and eligibility of studies shall be explained;

   (c) variables;

   (d) data sources: strategies and data sources for determining exposures, outcomes and all other variables relevant to the study objectives. Where the study will use an existing data source, such as electronic health records, any information on the validity of the recording and coding of the data shall be reported. In the case of a systematic review or meta-analysis, the search strategy and processes and any methods for confirming data from investigators shall be described;

   (e) study size: any projected study size, precision sought for study estimates and any calculation of the study size that can minimally detect a pre-specified risk with a pre-specified interpretative power;

   (f) data management;

   (g) data analysis;

   (h) quality control;

   (i) limitations of the research methods.

10. Protection of human subjects: safeguards in order to comply with national and Union requirements for ensuring the well-being and rights of participants in non-interventional post-authorisation safety studies.

11. Management and reporting of adverse events/adverse reactions and other medically important events while the study is being conducted.

12. Plans for disseminating and communicating study results.

13. References.

2. *Format of the abstract of the final study report*

1. Title, with subtitles including date of the abstract and name and affiliation of main author.

2. Keywords (not more than five keywords indicating the main study characteristics).

3. Rationale and background.

4. Research question and objectives.

5. Study design.

6. Setting.

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7. Subjects and study size, including dropouts.

8. Variables and data sources.

9. Results.

10. Discussion (including, where relevant, an evaluation of the impact of study results on the risk–benefit balance of the product).

11. Marketing authorisation holder.

12. Names and affiliations of principal investigators.

3. *Format of the final study report*

1. Title: title including a commonly used term indicating the study design; sub-titles with date of final report and name and affiliation of the main author.

2. Abstract: stand-alone summary referred to in Section 2 of this Annex.

3. Marketing authorisation holder: name and address of the marketing authorisation holder.

4. Investigators: names, titles, degrees, addresses and affiliations of the principal investigator and all co-investigators, and list of all collaborating primary institutions and other relevant study sites.

5. Milestones: dates for the following milestones:

(a) start of data collection (planned and actual dates);

(b) end of data collection (planned and actual dates);

(c) study progress reports;

(d) interim reports of study results, where applicable;

(e) final report of study results (planned and actual date);

(f) any other important milestone applicable to the study, including date of study registration in the electronic study register.

6. Rationale and background: description of the safety concerns that led to the study being initiated, and critical review of relevant published and unpublished data evaluating pertinent information and gaps in knowledge that the study is intended to fill.

7. Research question and objectives.

8. Amendments and updates to the protocol: list of any substantial amendments and updates to the initial study protocol after the start of data collection, including a justification for each amendment or update.

9. Research methods

9.1. Study design: key elements of the study design and rationale for this choice.

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9.2. Setting: setting, locations, and relevant dates for the study, including periods of recruitment, follow-up, and data collection. In the case of a systematic review or meta-analysis, study characteristics used as criteria for eligibility, with rationale.

9.3. Subjects: any source population and eligibility criteria for study subjects. Sources and methods for selection of participants shall be provided, including, where relevant, methods for case ascertainment, as well as number of and reasons for dropouts.

9.4. Variables: all outcomes, exposures, predictors, potential confounders, and effect modifiers, including operational definitions. Diagnostic criteria shall be provided, where applicable.

9.5. Data sources and measurement: for each variable of interest, sources of data and details of methods of assessment and measurement. If the study has used an existing data source, such as electronic health records, any information on the validity of the recording and coding of the data shall be reported. In the case of a systematic review or meta-analysis, description of all information sources, search strategy, methods for selecting studies, methods of data extraction and any processes for obtaining or confirming data from investigators.

9.6. Bias.

9.7. Study size: study size, rationale for any study size calculation and any method for attaining projected study size.

9.8. Data transformation: transformations, calculations or operations on the data, including how quantitative data were handled in the analyses and which groupings were chosen and why.

9.9. Statistical methods: description of the following items:

(a) main summary measures;

(b) all statistical methods applied to the study;

(c) any methods used to examine subgroups and interactions;

(d) how missing data were addressed;

(e) any sensitivity analyses;

(f) any amendment to the plan of data analysis included in the study protocol, with rationale for the change.

9.10. Quality control: mechanisms to ensure data quality and integrity.

10. Results: comprising the following subsections:

10.1. Participants: numbers of study subjects at each stage of study. In the case of a systematic review or meta-analysis, number of studies screened, assessed for eligibility and included in the review with reasons for exclusion at each stage.

10.2. Descriptive data: characteristics of study participants, information on exposures and potential confounders and number of participants with missing data. In the case of a systematic review or meta-analysis, characteristics of each study from which data were extracted.

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10.3. Outcome data: numbers of study subjects across categories of main outcomes.

10.4. Main results: unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision. Where relevant, estimates of relative risk shall be translated into absolute risk for a meaningful time period.

10.5. Other analyses.

10.6. Adverse events and adverse reactions.

11. Discussion

11.1. Key results: key results with reference to the study objectives, prior research in support of and conflicting with the findings of the completed post-authorisation safety study, and, where relevant, the impact of the results on the risk–benefit balance of the product.

11.2. Limitations: limitations of the study taking into account circumstances that may have affected the quality or integrity of the data, limitations of the study approach and methods used to address them, sources of potential bias and imprecision, and validation of the events. Both the direction and magnitude of potential biases shall be discussed.

11.3. Interpretation: interpretation of results, considering objectives, limitations, multiplicity of analyses, results from similar studies and other relevant evidence.

11.4. Generalisability.

12. References.