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IMPLEMENTING MEASURES IN ORDER TO HARMONISE THE PERFORMANCE OF THE PHARMACOVIGILANCE ACTIVITIES PROVIDED FOR IN DIRECTIVE 2001/83/EC AND REGULATION (EC) NO 726/2004

THE CONCEPT PAPER SUBMITTED FOR PUBLIC CONSULTATION

Deadline for Public Consultation: 7 November 2011

This document does not represent an official position of the European Commission. It is a tool to explore the views of interested parties on a preliminary draft. The suggestions contained in this document do not prejudge the form and content of any future proposal by the European Commission.

CONTACT:

Responses should be sent preferably by e-mail to sanco-pharmaceuticals@ec.europa.eu, or by post to Directorate-General for Health and Consumers, Unit SANCO/D/3, BE-1049 Brussels. The subject of the letter/e-mail should refer to "PCIM/11/01 - Public Consultation on implementing measures for pharmacovigilance".

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I. ABOUT THE CONSULTATION

A. INTRODUCTION

In order to harmonise the performance of the new pharmacovigilance activities introduced by the amended pharmacovigilance legislation the Commission shall pursuant to Directive 2010/84/EU amending Directive 2001/83/EC and Regulation (EU) No 1235/2010 amending Regulation (EC) No 726/2004 adopt several implementing measures covering the following topics:

(a) The content and maintenance of the pharmacovigilance system master file kept by the marketing authorisation holder;

(b) The minimum requirements for the quality system for the performance of pharmacovigilance activities by the national competent authorities, the European Medicines Agency (EMA) and the marketing authorisation holder;

(c) The use of internationally agreed terminology, formats and standards for the performance of pharmacovigilance activities;

(d) The minimum requirements for the monitoring of data in the Eudravigilance database to determine whether there are new risks or whether risks have changed;

(e) The format and content of the electronic transmission of suspected adverse reactions by Member States and the marketing authorisation holder;

(f) The format and content of electronic periodic safety update reports and risk management plans;

(g) The format of protocols, abstracts and final study reports for the post-authorisation safety studies.

Those measures supplement essential aspects of the new pharmacovigilance system with the more technical details that have to be observed by marketing authorisation holders, national competent authorities and EMA in the daily practice of applying the new legislation. It is therefore important that they are fit for purpose and strike the necessary balance between the fundamental objective of the current legislative framework for medicinal products, i.e. to safeguard public health, and general internal market requirements.

The purpose of this consultation paper is therefore to describe the scope and content of the implementing measures the Commission is currently considering and to seek views and feedback from stakeholders on those issues.

This concept paper is now being put out for public consultation. Replies or comments should be submitted by 7 November 2011 at the latest.

B. CONSULTATION TOPICS

1. ONE GLOBAL IMPLEMENTING MEASURE

In the Commission's view it is appropriate to address all different implementing measures in one global implementing measure that supplements Directive 2001/83/EC and Regulation (EC) No 726/2004 as regards the performance of pharmacovigilance activities from July 2012 onwards, when the new rules are applicable.

This will lead to a more transparent set of rules and avoid any overlap between different implementing acts.

The present document is based on a detailed technical contribution that the Commission received from a dedicated project team of experts from Member States and the European Medicines Agency for which the Commission is grateful. This means however, at the same time, that the present document does not necessarily represent in all parts the position of the European Commission. Instead, it is a tool to explore the views of interested parties on a preliminary proposal.

In view of the level of detail and the technicalities that the final implementing measures should offer, it was nevertheless felt appropriate to limit the paper not just to the presentation of general concepts, but instead to be precise on those details and subsequent obligations. As a consequence a specific format, including numbering, structure and tense, has been used for the concept paper, which will also ease reading, streamline the process and facilitate commenting. This format does however neither prejudge the form and content of any future proposal by the European Commission, nor should it prevent stakeholders from commenting on specific aspects of the document.

With the entering into force of the new implementing measure, Commission Regulation (EC) No 540/95 will be superseded as far as human medicinal products are concerned.

2. SPECIFIC CONSULTATION ITEMS

The consultation text is supplemented by several specific consultation items in boxed text raising certain questions on which the Commission seeks the input from interested parties.

Respondents are invited to specifically address those points. However, in addition, comments on all parts and aspects of this implementing measure are appreciated.

C. HOW CAN I CONTRIBUTE?

Stakeholders are invited to comment on this consultation paper, and especially on the boxed text, by 7 November 2011 at the latest. Responses should be sent preferably by e-mail to sanco-pharmaceuticals@ec.europa.eu, or by post to Directorate-General for Health and Consumers, Unit SANCO/D/3, BE-1049

Brussels. The subject of the letter/e-mail should refer to "PCIM/11/01 - Public Consultation on implementing measures for pharmacovigilance".

When sending your comments and responses, you should state whether you are a stakeholder association or a private individual. If you represent an association, please indicate clearly what type of association this is (patients, health professionals, manufacturers, marketing authorisation holders etc.). If you represent a company, please state whether it falls within the EU definition of a small and medium-sized enterprise (i.e. less than €50 million annual turnover and fewer than 250 employees).

An acknowledgement of receipt will be issued for each contribution received.

The received contributions together with the identity of contributors will be made publicly available on the 'public health' website[1], unless the contributor objects to publication of his or her personal data on the grounds that such publication would harm his or her legitimate interests. In this case the contribution may be published in anonymous form. Otherwise the contribution will not be published nor will, in principle, its content be taken into account. For more information on the processing of your personal data in the context of this consultation, read the specific Privacy Statement available on the dedicated consultation page on the public health website.

Professional organisations are invited to register in the Union's Register for Interest Representatives (http://ec.europa.eu/transparency/regrin/) set up as part of the European Transparency Initiative to provide the Commission and the public at large with information about the objectives, funding and structures of interest representatives.

D. WHAT WILL HAPPEN NEXT?

All contributions will be carefully analysed. The implementing Regulation will build on the consultation.

[1] http://ec.europa.eu/health/human-use/index_en.htm.

II. THE CONCEPT PAPER SUBMITTED FOR CONSULTATION

A. Pharmacovigilance system master file

1. Definition

The pharmacovigilance system master file contains a detailed description of the pharmacovigilance system used by the marketing authorisation holder with respect to one or more authorised medicinal products.

For different categories of medicinal products the marketing authorisation holder may, if appropriate, apply separate pharmacovigilance systems. Each system must be then described in a separate pharmacovigilance master file. Those files shall cumulatively cover all authorised products of the marketing authorisation holder.

2. Location

The pharmacovigilance system master file shall be located at the site where the qualified person responsible for pharmacovigilance operates. The marketing authorisation holder should ensure that the qualified person for pharmacovigilance has permanent access to the pharmacovigilance system master file.

Without prejudice to other requirements any change in its location shall be notified immediately after the implementation to EMA in accordance with Article 57(2)(c) of Regulation (EC) No 726/2004 in order to correct the information on the European medicines web-portal.

3. Content

The pharmacovigilance master file shall include essential documents to describe the pharmacovigilance system, especially the following:

(1) A list of medicinal products relevant to the pharmacovigilance system master file including the name of the medicinal product, international non-proprietary name (INN) of active substance(s), procedure under which the product have been authorised, authorisation number, Member State(s) in which the authorisation is valid including information on whether the medicinal product has been actually placed on the market.

(2) Information relating to the qualified person for pharmacovigilance including:

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

(b) qualifications, experience and registrations relevant to pharmacovigilance;

(c) contact details; and

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

(3) Information relating to the contact person for pharmacovigilance where nomination at national level has been made in accordance with Article 104(4) of Directive 2001/83/EC, including contact details and a description of responsibilities.

(4) Description of the organisational structure of the marketing authorisation holder, including the list of the site(s) where the pharmacovigilance functions are undertaken covering individual case safety report collection, evaluation, safety database case entry, periodic safety update report production, signal detection and analysis, risk management plan management, pre-an post authorisation study management and safety variations to product particulars.

(5) A description of the location, functionality and operational responsibility for computerised system and databases used to receive, collate, record and report safety information and of assessment of their fitness for purpose.

(6) A description of the process, data handling and records for the fulfilment of pharmacovigilance in the following aspects:

(a) Continuous monitoring of product benefit-risk profile(s) applied and the result of evaluation;

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

(c) Individual case safety report collection, assessment and reporting;

(d) Periodic safety update report production and submission;

(e) Process for communicating safety concerns and safety variations to the summary of product characteristics and package leaflet to patients and health professionals.

Consultation item no. 1: Should additional processes and pharmacovigilance tasks be covered?

(7) A description of the quality system for the performance of pharmacovigilance activities including:

(a) List of documented procedures and processes related to pharmacovigilance activities and interfaces with other functions, with reference to their location;

(b) A description of the resource management for the performance of pharmacovigilance activities;

(c) Reference to the location of training files and records of qualification for individuals performing pharmacovigilance tasks;

(d) Documentation arrangements and the location of any records in relation to pharmacovigilance activities;

(e) Reference to the location of audit trails concerning the monitoring of the performance and the compliance of the main outputs of the pharmacovigilance system.

4. Maintenance

The information in the pharmacovigilance system master file should be succinct, accurate and reflect the current system in place. It shall be continuously kept up to date and, where necessary, shall be revised to take account of experience gained, technical and scientific progress and amendments in the legislative requirements.

Consultation item no. 2: The aim of the pharmacovigilance master file is two-fold: to concentrate information in one global document and to facilitate maintenance by uncoupling it from the marketing authorisation. Therefore changes to the content of the master file will be no longer subject to variation obligations. Would it be nevertheless appropriate to require the marketing authorisation holder to notify significant changes/modifications to the master file to the competent authorities in order to facilitate supervision tasks? If so, how should this be done? Should the master file contain a date when it was last reviewed?

5. Documentation

Pharmacovigilance system master file documents shall be complete and legible. If appropriate, information may be provided in form of charts or flow diagrams. All documents shall be indexed and archived in a way that ensures that all documentation is readily available.

The pharmacovigilance master file may be stored/hold in electronic form on condition that a clearly arranged printed copy can be made available for audits and inspections.

Any current deviations from the pharmacovigilance procedures, their impact and management should be noted until resolved.

The master file shall contain a logbook recording any alteration of its content within the last five years. This logbook should record the date, the responsible person and where appropriate the reason for the alteration.

6. Delegation

The marketing authorisation holder may delegate certain tasks of the pharmacovigilance system to third parties. He nevertheless retains full responsibility for the completeness and accuracy of the pharmacovigilance system master file.

In those cases the pharmacovigilance system master file shall contain a description of the delegated activities and/or service provisions relating to the fulfilment of pharmacovigilance obligation, indicating the parties involved, roles undertaken and concerned product(s) and territory(ies). Copies of the signed agreements shall be included in the master file.

Consultation item no. 3: Is it necessary to be more precise on potential delegation, e.g. in the case of co-marketing of products? Please comment.

7. Audit

All completed audits of the pharmacovigilance activities of the marketing authorisation holder shall be recorded in an annex to the pharmacovigilance master file, including their date and scope.

Immediately after an audit report has been received that requires corrective or preventive action, the marketing authorisation holder shall place a note concerning the main findings of the audit on the pharmacovigilance master file. That note may be removed once the corrective and preventive actions have been fully implemented, which is taken to mean that correction and/or sufficient improvement can be demonstrated or has been verified.

Consultation item no. 4: Should a copy of the audit report be retained in the master file? Would it be appropriate to require documentation of audit schedules?

8. Inspection

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

The national competent authority and EMA may at any time ask the marketing authorisation holder to submit a copy of the pharmacovigilance system master file. The marketing authorisation holder shall submit the copy at the latest seven days after receipt of the request at its own expenses.

Consultation item no. 5: Overall, do you agree with the requirements as regards the content and maintenance of the pharmacovigilance master file? Please comment.

B. Quality systems for the performance of pharmacovigilance activities – Common obligations

9. Scope

Marketing authorisation holders, the national competent authorities and EMA must establish and follow a quality system adequate and effective for the purpose of performing their pharmacovigilance activities.

The quality system covers the organisational structure, responsibilities, procedures, processes and resources and requires an appropriate resource management, compliance management and record management.

The quality system shall follow a cycle of:

(a) Establishing structures and planning integrated and consistent processes;

(b) Carrying out the tasks and responsibilities;

(c) Monitoring and evaluating how effectively the structures and processes have been established and how effectively the processes are carried out; and

(d) Correcting and improving the structures and processes and the conduct of those processes as necessary.

All elements, requirements and provisions adopted for the quality system must 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.

10. Audit

Audits of the quality system shall be performed at regular intervals, and not less than every two years, to assure that the quality system is in compliance with the established quality system requirements and to determine its effectiveness. Quality audits shall be conducted by individuals who do not have direct responsibility for the matters being audited.

Corrective action(s), including a reaudit of deficient matters, shall be taken when necessary. A report of the results of each quality audit, and reaudit(s) where taken, shall be made and such reports shall be reviewed by management having responsibility for the matters audited. The dates and results of quality audits and reaudits shall be documented.

11. Performance indicators

Where indicators are used to continuously monitor the good performance of pharmacovigilance activities, those indicators and their results shall be documented. For marketing authorisation holders this shall be done in an annex to the pharmacovigilance system master file.

EMA may publish after the consultation of the Pharmacovigilance Risk Assessment Committee a list of performance indicators.

C. Quality systems for the performance of pharmacovigilance activities by marketing authorisation holders

12. General

The quality system shall be recognised as being the responsibility of all persons involved in the relevant processes of the marketing authorisation holder with management ensuring a systematic approach towards quality and the implementation and maintenance of the quality system.

The quality system shall fulfil the following minimum requirements:

13. Resource management

A sufficient number of competent and appropriately qualified and trained personnel shall be available in the operation of pharmacovigilance activities. In that context, it shall be ensured that the qualified person for pharmacovigilance has acquired adequate theoretical and practical knowledge for the performance of pharmacovigilance activities. If the qualified person is not medically qualified, access to a medically qualified person should be available.

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

All personal involved in the performance of pharmacovigilance activities shall receive initial and continued training. Training plans and records for documenting and maintaining and developing the competences of personal shall be kept and made available for audit or inspection.

Appropriate instructions on critical processes, including business continuity, shall be provided.

The resource management shall be documented in the pharmacovigilance system master file.

14. Compliance management

Specific quality system procedures and processes shall be in place in order to:

(a) ensure that that pharmacovigilance data is continuously monitored and that all information referred to in Article 101(1) of Directive 2001/83/EC is evaluated scientifically, that options for risk minimisation and prevention are considered and that appropriate measures are taken as necessary. The marketing authorisation holder must follow-up such information independent of its source, including information spontaneously reported by patients or healthcare professionals, or occurring in the context of a post-authorisation study.

(b) ensure that data on serious and non-serious adverse reactions are submitted to the Eudravigilance database within the timelines stipulated by Article 107 of Directive 2001/83/EC.

(c) ensure an effective communication with the competent authorities and EMA, including communication on pharmacovigilance system master files, risk management systems, risk minimisation measures, periodic safety update reports and post-authorisation studies.

(d) ensure that the product information is kept up to date with the current scientific knowledge, including the conclusions of the assessment and recommendations made public by means of the European medicines web-portal. To this end, the marketing authorisation holder shall check the European medicines web-portal for any relevant updates, including consultations and notifications of procedures, on each working day.

(e) ensure that any information on pharmacovigilance submitted to the competent authorities and EMA in relation to products of the marketing authorisation holder shall be correct and complete.

Consultation item no. 6: Is there a need for additional quality procedures, e.g. in relation to study reporting in accordance with Article 107p of the Directive, in relation to communication on pharmacovigilance between the marketing authorisation holder and patients/health professionals; in relation to processes for taking corrective and improvement actions or in relation to the detection of duplicates of suspected adverse reaction reports in the Eudravigilance database?

Where a marketing authorisation holders has delegated certain tasks of its pharmacovigilance activities he retains responsibility that an effective quality system is applied in relation to those tasks.

15. Record management

A quality system shall be in place for maintaining a record management system for all documents used for pharmacovigilance activities, ensuring the retrievability of these documents as well as traceability of how safety concerns have been investigated, the timelines for these investigations and how and when decisions have been taken. In this context, marketing authorisation holders shall establish mechanisms enabling traceability and follow-up of adverse reaction reports while complying with data protection legislation.

Pharmacovigilance system-related documents shall be retained as long as the system as described in the pharmacovigilance master file exists and for a further 10 years after it has ceased to exist. Product-related documents shall be retained as long as the marketing authorisation exists and for further at least 30 years after the marketing authorisation has ceased to exist.

Documentation arrangements, including the location of records, shall be documented in the pharmacovigilance master file.

Consultation item no. 7: Do you agree with the requirements for marketing authorisation holders? Please comment.

D. Quality systems for the performance of pharmacovigilance activities by national competent authorities and EMA

16. General

Quality systems shall be recognised as being the responsibility of all persons involved in the relevant processes of the national competent authority and EMA ensuring a systematic approach towards quality and the implementation and maintenance of the quality system.

The quality system shall fulfil the following minimum requirements:

17. Resource management

A sufficient number of competent and appropriately qualified and trained personnel shall be available in the operation of pharmacovigilance activities.

The organisational structures and assignment of tasks and responsibilities shall be clearly determined and, to the extent necessary, accessible to facilitate interaction between national competent authorities, EMA, marketing authorisation holders and persons reporting information in accordance with Article 101(1) of Directive 2001/83/EC. To this end, contact points shall be established.

All personal involved in the performance of pharmacovigilance activities shall receive initial and continued training. Training plans and records for documenting and maintaining and developing the competences of personal shall be kept and made available for audit.

Appropriate instructions on critical processes, including business continuity, shall be provided.

18. Compliance management

Specific quality system procedures and processes shall be in place in the national competent authorities and in EMA in order to:

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

(b) assess pharmacovigilance data and process it in accordance with the timelines provided by Directive 2001/83/EC;

(c) ensure effective communication within the Union regulatory network as well as with patients, healthcare professionals, marketing authorisation holders and the general public;

(d) guarantee that national competent authorities and EMA inform each other and the Commission not less than 24 hours prior to public announcements relating to information on pharmacovigilance concerns and to allow for coordination of the content of the safety announcement in case of a medicinal product or an active substance contained in medicinal products authorised in more than one Member State; and

(e) conduct inspections, including pre-authorisation inspections.

Additionally, national competent authorities shall have quality system procedures for:

– collecting and recording all suspected adverse reactions that occur in their territory.

EMA shall have additional quality system procedures for:

– literature monitoring in accordance with Article 27 of Regulation (EC) 726/2004.

19. Record management

Quality systems shall be in place for maintaining a record management system for all documents used for pharmacovigilance activities, ensuring the retrievability of these documents as well as traceability of how safety concerns have been investigated, the timelines for these investigations and how and when decisions have been taken.

At each stage of storage and processing of pharmacovigilance data, measures should be taken to ensure data security and confidentiality. This involves strict control of access to documents and to databases to authorised personnel sharing the medical and administrative confidentiality of the data.

Use of terminologies should be monitored and validated, either systematically or by regular random evaluation. Data entry staff should be instructed in the use of the terminologies, and their proficiency verified.

Pharmacovigilance system-related documents shall be retained as long as the system as described in the pharmacovigilance master file exists and for a further 10 years after it has ceased to exist. Product-related documents shall be retained as long as the marketing authorisation exists and for further at least 30 years after the marketing authorisation has ceased to exist.

Consultation item no. 8: Do you agree with the quality system requirements? Please comment, if appropriate separately as regards requirements for marketing authorisation holders, national authorities and EMA.

E. Signal detection and risk identification

20. General

EMA and national competent authorities shall collaborate to monitor the data available in the Eudravigilance database for medicinal products authorised in the Union used within the terms of the marketing authorisation as well as outside the terms of the marketing authorisation, and for medicinal products authorised in the Union that may induce an occupational exposure.

The marketing authorisation holders shall monitor the data to the extent of their accessibility to the Eudravigilance database, as part of their broader monitoring of all emerging data and global signal detection activities. Marketing authorisation holders shall inform EMA and national competent authorities in the event of new risks or risks that have changed or when changes to the risk-benefit balance have been detected.

21. Changed risks/new risks

The identification of new risks or changed risks is based on the detection and analysis of the relevant signals. To this end, a signal consists of information that arises from one or multiple sources (including observations and experiments), which suggest 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, that is judged to be of sufficient likelihood to justify verificatory action.

The detection of a signal shall be based on multidisciplinary based approach and be supported by statistical analysis within Eudravigilance. Following consultation of the Pharmacovigilance Risk Assessment Committee EMA may publish a list of medical events that have to be taken into account for the detection of a signal.

22. Methodology

In order to determine the evidence contained in a signal a common methodology shall be applied taking account of the quantitative strength of the association, consistency of the data, exposure response relationship, biological plausibility, experimental findings, possible analogies and the nature and quality of the data.

It may be distinguished between different types of factors related to the selection of signals, namely the fact 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 the reports to the Eudravigilance database.

The Pharmacovigilance Risk Assessment Committee shall perform a regular review of the methodology to be used and publish recommendations, if appropriate.

23. Signal management procedure

Marketing authorisation holders, national competent authorities and EMA shall ensure continuous monitoring of the Eudravigilance database with a frequency proportionate to the identified risk, the potential risks and the need for additional information.

National competent authorities shall specifically monitor data originated in their territory.

Any signal that has been communicated to EMA or the national competent authorities by the marketing authorisation holder shall be validated to determine whether further analysis is required. For products authorised in accordance with Directive 2001/83/EC that validation shall be done by the national competent authorities. For products authorised in accordance with Regulation (EC) No 726/2004 validation shall be done by EMA.

Any validated signal that requires further analysis shall be entered into the tracking system administered by EMA and shall be transmitted to the Pharmacovigilance Risk Assessment Committee in order to perform the initial analysis and prioritisation of signals and to consider follow-up action in accordance with Article 107h(2) of Directive 2001/83/EC.

24. Work sharing of signal management

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 by Article 27 of Directive 2001/83/EC to appoint a lead Member State for the monitoring of data in the Eudravigilance

database. All Member States retain however, their responsibility pursuant to Article 107h(1)(c) and (3) of Directive 2001/83/EC.

When appointing a lead Member State, the coordination group shall 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 lead Member State for the assessment of periodic safety update reports in accordance with Article 107(e) of Directive 2001/83/EC.

EMA shall make public a list of active substances and of the lead Member State appointed for their monitoring in Eudravigilance.

Consultation item no. 9: For efficiency reasons a 'work sharing' procedure could be appropriate for the monitoring of medicinal products or active substances contained in several medicinal product. However, do you see a risk in cumulating all tasks (for the authorisation, PSUR scrutiny and Eudravigilance monitoring) in one Member State, as thereby the benefits of parallel monitoring may be lost ("peer review" system)? Additionally, it may be envisaged to extend 'work sharing' to all medicinal products (including all centrally approved products) and to appoint a lead Member State in addition to EMA (Article 28a(1)(c) of Regulation (EC) No 726/2004). Please comment.

25. Signal detection support

EMA shall support the monitoring of the Eudravigilance database by providing access to:

– data outputs and statistical reports allowing a review of new adverse reactions and of all adverse reactions reported to Eudravigilance in relation with an active substance or a medicinal product;

– customised queries supporting the evaluation of individual case safety reports and case series;

– 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;

– statistical signal detection methods.

26. Signal detection audit

The national competent authorities and EMA shall keep an audit trail of their signal detection activities in Eudravigilance and of the relevant queries and their outcomes. The audit trail shall allow traceability of how signals have been detected and how validated signals have been investigated.

Consultation item no. 10: In the Commission's view the aim of this part is to establish common triggers for signal detection; to clarify the respective monitoring roles of marketing authorisation holders, national competent authorities and EMA; and to identify how signals are picked up? Are the proposed provision sufficiently clear and transparent or should they be more detailed? If so, which aspects require additional considerations and what should be required? Please comment.

F. Use of terminology

27. Use of internationally agreed terminology

For the purpose of classification, retrieval, presentation, benefit-risk evaluation and assessment, electronic exchange as well as communication of pharmacovigilance and medicinal product information, Member States, marketing authorisation holders and EMA shall apply the following internationally agreed terminology:

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

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

(c) The terminology resulting from and supporting the implementation of ISO EN 11615, Health Informatics, Identification of Medicinal Products (IDMP) standard, 'Data elements and structures for unique identification and exchange of regulated medicinal product information'.

(d) The terminology resulting from and supporting the implementation of ISO EN 11616 Health Informatics, Identification of Medicinal Products (IDMP) standard, 'Data elements and structures for unique identification and exchange of regulated pharmaceutical product information'.

(e) The terminology resulting from and supporting the implementation of ISO EN 11238 Health Informatics, Identification of Medicinal Products (IDMP) standard, 'Data elements and structures for unique identification and exchange of regulated information on substances'.

(f) The terminology resulting from and supporting the implementation of ISO EN 11239 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'.

(g) The terminology resulting from and supporting the implementation of ISO EN 11240 Health Informatics, Identification of Medicinal Products (IDMP) standard, 'Data elements and structures for unique identification and exchange of units of measurement'.

The terminology according to lit. (c) to (g) shall be applied as of 1 January 2015.

In the event that a required term is not available, Member States or marketing authorisation holders shall make a request for the addition of a new term to the organisation that is responsible for maintaining the terminology and inform EMA accordingly.

Consultation item no. 11: Do you agree with the proposed terminology? Please comment.

28. Use of internationally agreed formats and standards

For the purpose of describing, retrieval, presentation, benefit-risk evaluation and assessment, electronic exchange as well as communication of pharmacovigilance and medicinal product information, the following internationally agreed formats and standards shall be applied by Member States, marketing authorisation holders and EMA:

(a) ISO EN 27953-2 Health Informatics, 'Individual Case Safety Reports' for the electronic transmission of suspected adverse reactions.

(b) ISO EN 11615, Health Informatics, Identification of Medicinal Products (IDMP) standard, 'Data elements and structures for unique identification and exchange of regulated medicinal product information'.

(c) ISO EN 11616, Health Informatics, Identification of Medicinal Products (IDMP) standard 'Data elements and structures for unique identification and exchange of regulated pharmaceutical product information'.

(d) ISO EN 11238, Health Informatics, Identification of Medicinal Products (IDMP) standard, 'Data elements and structures for unique identification and exchange of regulated information on substances'.

(e) ISO EN 11239, 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'.

(f) ISO EN 11240, Health Informatics, Identification of Medicinal Products (IDMP) standard, 'Data elements and structures for unique identification and exchange of units of measurement'.

(g) ICH M2 Recommendations 'Procedure'.

(h) ICH M2 Recommendations 'ESTRI Gateway'.

(i) ICH M2 Recommendation 'File Format PDF'.

(j) ICH M2 Recommendation 'File Format XML'.

(k) ICH M2 Recommendation 'Information Transfer EDIINT AS1'.

The formats and standards according to lit. (a) to lit. (f) shall be applied as of 1 January 2015.

Until the date of application of the formats and standards referred to in lit. (a) to lit.(f) the following formats and standards shall be applied:

(a) the EudraVigilance Medicinal Product Report Message (EVPRM). The EVPRM refers to the format for the electronic submission of information on all medicinal products for human use authorised in the Union in accordance with Article 57, paragraph 2, second sub-paragraph of Regulation (EC) No 726/2004 as published by EMA.

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

(c) ICH M2 standard ‘Electronic Transmission of Individual Case Safety Reports Message Specification’ (ICH ICSR DTD version 2.1).

Consultation item no. 12: Do you agree with the list of internationally agreed formats and standards? Please comment.

G. Transmission and Submission requirements

29. Transmission of suspected adverse reactions

Electronic transmissions of suspected adverse reactions by Member States and the marketing authorisation holder shall be made in accordance with Annex I.

30. Risk management plans

Risk management plans shall be submitted in accordance with Annex II.

31. Periodic safety update reports and

Electronic periodic safety update reports shall be submitted in accordance with Annex III.

32. Post authorisation safety studies

Protocols, abstracts and final study reports for non-interventional post-authorisation safety studies shall be submitted in accordance with Annex IV.

Consultation item no. 13: Is there additionally a need for transitional provisions as regards certain aspects of this implementing measure, especially in relation to the specifications on format and content? Please comment.

Annex I – Electronic submissions of suspected adverse reactions

1. Definitions

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

1. Adverse reaction reports include reports on noxious and unintended effects from the authorised use of a medicinal product but also from:

(a) Use outside the terms of the marketing authorisation including misuse and abuse. Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the prescribed or authorised dose, route of administration and/or indication(s) or where a prescription only medicinal product was used without a prescription. Abuse refers to the sporadic or persistent, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

(b) Medication error, which refers to inappropriate use of a medicinal product while in the control of the healthcare professional, patient, or consumer.

(c) Overdose, which refers to the administration of a quantity of a medicinal product given per administration or per day, which is above the maximal recommended dose according to the authorised product information. This shall also take into account cumulative effects due to overdose.

(d) Occupational exposure, which refers to the exposure to a medicinal product for human use as a result of one's occupation.

2. Individual Case Safety Report (ICSR) refers to the format and content for the reporting of one or several suspected adverse reactions in relation to a medicinal product that occur in a single patient at a specific point of time. A valid ICSR for expedited reporting shall include at least an identifiable reporter, an identifiable patient, at least one suspect adverse reaction and a suspect medicinal product.

2. Format of electronic transmission of suspected adverse reactions

Member States and marketing authorisation holders shall use the agreed format and terminology for electronic transmission of suspected adverse reactions.

3. Content of electronic transmission of suspected adverse reactions

1. Member States and marketing authorisation holders shall ensure that all individual cases are well documented and Individual Case Safety Reports are as complete as possible when transmitted electronically to the Eudravigilance database, providing all information which is available upon initial receipt and any subsequent follow-up with the reporter in an accurate and reliable manner.

2. Member States and marketing authorisation holders shall record sufficient details necessary for obtaining follow-up information of adverse reaction reports as outlined in

Articles 107a(1), (2) and 107(4) of Directive 2010/83/EC. Follow-up of reports shall be adequately documented.

3. To detect, assess, understand and prevent adverse reactions and to identify and take actions to reduce the risks of, and increase the benefits from, medicinal products for the purpose of safeguarding public health, the processing of personal data within the Eudravigilance system is possible while respecting Union legislation relating to data protection. Pseudonymisation may be applied by Member States and marketing authorisation holders to facilitate the processing of personal data thereby replacing Personally Identifiable Information such as name and address with pseudonyms.

4. For the purpose of electronic reporting of suspected adverse reactions, Member States and marketing authorisation holders shall provide all available information on each individual case, in particular:

(a) Administrative information: report type, date and a world-wide unique case identification number as well as unique sender identification and sender type. The date the report was first received from the source and the date of the receipt of the most recent information using a precise date. Other case identifiers and their source, as well as reference 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[2] for adverse reactions reported in the world-wide literature. A copy of the relevant literature article including a comprehensive English summary of the article. Upon request of EMA, a full translation of the article, if required, shall be provided by the marketing authorisation holder that transmitted the initial report.

(c) Study type, study name and the sponsor study number or study registration number for reports from studies not covered by EU legislation on clinical trials (Directive 2001/20/EC).

(d) Primary source(s), which refers to the person(s) who reports the facts: reporter identifiable information including Member State and qualification.

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

(f) Relevant medical history and concurrent conditions and relevant past medicinal product history.

(g) Suspect/interacting medicinal product(s). Medicinal product(s) shall be reported by the name in accordance with Article 1(20) of Directive 2001/83/EC and where this is not available, by the active substance(s) and any other characteristics that allow for the identification of the medicinal product(s) such as: name of the marketing

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

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) shall be reported. A follow-up procedure shall be in place to obtain this information, if not available in the initial report.

(i) Concomitant medicinal products and past-medical drug therapy for the patient (and for the parent), where applicable. The reporting of this information shall follow the principles as set out above under g).

(j) Suspected adverse reaction(s): start date and end date of the suspected adverse reaction(s) and/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 and the original reporter's words and/or short phrases used to describe the reaction(s).

(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 case of death of the patient.

(m) A case narrative providing all relevant information for individual cases where a serious adverse reaction(s) is/are reported by marketing authorisation holders. 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. It shall be confirmed that no additional information is available.

(n) Reason for nullification or amendment for nullification and amendment reports.

(o) For narrative and textual descriptions, where reported in an official language in the EU other than English, an English summary with the initial verbatim text. For suspected adverse reactions originating outside the EU, English shall be used for adverse reaction reporting.

Consultation item no. 14: Do you agree with the proposed format and content? Please comment.

Annex II – Risk management plans

1.1. Content of the Risk Management Plan

Pursuant to Article 1 point 28c of Directive 2001/83/EC a risk management plan contains a detailed description of the risk management system. To this end, it shall:

- Identify or characterise the safety profile of the medicinal product(s) concerned;
- Describe how the safety profile will be assessed and monitored;
- Document measures in place to prevent or minimise the risks associated with the medicinal product including the assessment of the effectiveness of those interventions.

Products containing the same active substance and belonging to the same marketing authorisation holder should be included, if appropriate, in one Risk management plan.

1.2. Format of the Risk Management Plan

The risk management plan (RMP) shall consist of seven parts, which may be subdivided, and will include the following modules:

Part I: Product(s) Overview

Part II: Safety Specification

Module I: Epidemiology of the indications and target population

Module I: Non-clinical part of the Safety Specification

Module III: Clinical trial exposure

Module IV: Populations not studied in clinical trials

Module V: Post Authorisation Experience

Module VI: Identified and potential risks

Module VII: Additional EU Requirements for the Safety Specification

Module VIII: Summary of the safety concerns

Part III: Pharmacovigilance Plan

Part IV: Plans for studies on effectiveness and long term efficacy

Part V: Risk Minimisation measures

Part VI: Summary of the RMP

Part VII: Annexes

Where a RMP covers several medicinal products, a separate Part VI shall be provided for each medicinal product.

Part VI of the RMP shall be made publicly available in accordance with Article 106(c) of Directive 2001/83/EC and Article 26(1)(c) of Regulation (EC) No 726/2004 as amended. The summary should include key elements of the risk management plan addressing important potential and identified risks as well as missing information. A summary of risk minimisation activities should also be included.

Without prejudice to the requirement to submit a RMP as part of the Common Technical Document, for centrally authorised products and, where appropriate, nationally authorised products, the RMP shall be submitted electronically and in an electronic format specified by EMA and national competent authorities and published on their websites. The Marketing Authorisation Holder is responsible for ensuring that the electronic version and the Common Technical Document are consistent with each other.

1.3. Updates of the Risk management plan

1. If a RMP has previously been submitted for the medicinal product, the submission shall be in the form of an update.

2. Each submission of the RMP shall have a distinct version number and shall be dated.

Consultation item no. 15: Do you agree with the proposed format and content? Please comment.

Annex III – Electronic periodic safety update reports

1.1. Content of the periodic safety update reports

1. Pursuant to Article 107b of Directive 2001/83/EC, periodic safety update reports (PSURs) submitted by the Marketing Authorisation Holder (MAH), shall contain a scientific evaluation of the risk-benefit balance of the medicinal product, which shall be based on all available data.

2. A PSUR shall contain cumulative data starting from the granting of the marketing authorisation while retaining a focus on new information emerging in the period since the last PSUR submission.

3. PSURs shall provide an accurate estimation of the population exposed to the medicinal product including all data relating to the volume of sales and volume of prescriptions. This accurate estimation of exposure will be accompanied by a qualitative and quantitative analysis of actual use including how it may differ from indicated use based on all data available to the Marketing Authorisation Holder including the results of observational or drug utilisation studies.

4. Results of assessments of the effectiveness of risk minimisation activities relevant to the risk-benefit assessment shall be included.

5. Detailed listings of individual cases shall not be included routinely. Case narratives shall however, be provided where relevant to the scientific analysis of a signal or safety concern in the relevant risk evaluation section of the PSUR.

6. Unless otherwise specified in the list of union reference dates and frequency of submission, a single PSUR shall be prepared for all medicinal products containing the same active substance, authorised to one MAH, including all indications, routes of administration, dosage forms and dosing regimens, irrespective of whether authorised under different names and through separate procedures. When relevant, data relating to a particular indication, dosage form, route of administration or dosing regimen should be presented in a separate section within the body of the PSUR and any safety concerns addressed accordingly without preparing a separate PSUR.

7. Unless otherwise specified in the list of union reference dates and frequency of submission two options are foreseen for products containing the same combination of active substances. The MAH shall either submit stand-alone PSUR for the combination of active substances with cross-reference to the single-substance PSUR(s), authorised to the same MAH or provide the combination data within one of the single active substance PSURs.

1.2. Format of the Periodic safety update reports

1. Without prejudice to the requirement to submit a PSUR as part of the Common Technical Document, for centrally authorised products and, where appropriate, nationally authorised products, the PSUR shall be submitted electronically according to the following modular structure:

- Signature Page by the qualified person responsible for pharmacovigilance
- Title Page
- Table of contents
- Executive Summary

1. Introduction

2. Worldwide Marketing Approval Status

3. Actions Taken in the Reporting Period for Safety Reasons

4. Changes to Reference Safety Information

5. Estimated Exposure

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 Spontaneous Data Sources

7. Summaries of Significant Findings from Clinical Trials in the Reporting Period

7.1. Completed Clinical Trials

7.2. Ongoing Clinical Trials

7.3. Long-term Follow-up

7.4. Other Therapeutic Use of Investigational Drug

7.5. New Safety Data Related to Combination Therapies

8. Findings from Non-interventional Studies

9. Other Clinical Trial/Study Information

10. Non-clinical Data

11. Literature

12. Other Periodic Reports

13. Lack of Efficacy in Controlled Clinical Trials

14. Late Breaking Information

15. Overview of Signals Ongoing and Closed

16. Signal and Risk Evaluation

    16.1. Summaries of Safety Issues

    16.2. Signal Evaluation

    16.3. Evaluation of Risks and New Information

    16.4. Characterisation of Risks

    16.5. Effectiveness of Risk Minimisation

17. Benefit Evaluation

    17.1. Important Efficacy and Effectiveness Information

    17.2. Newly Identified information on Efficacy and Effectiveness

18. Integrated Benefit-risk Analysis for Approved Indications

    18.1. Introduction

    18.2. Discussion on the Benefit-risk Balance

19. Conclusions and Actions

20. Region-specific Information

21. Appendices to the PSUR

2. EMA may publish appropriate templates on the individual modules.

Consultation item no. 16: Do you agree with the proposed format and content? Please comment.

Annex IV – Protocols, abstracts and final study reports for the post-authorisation safety studies

1. Scope and Definitions

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

2. The 'date at which a study commences' is the date of the start of data collection.

3. 'Start of data collection' means the date at which information on the first study patient is first recorded in the study dataset or, in case of secondary use of data, the date at which the data extraction starts.

4. 'End of data collection' means the date at which the analytical dataset is first available.

5. All studies referred to in paragraph (1) shall have a written study protocol. Prior to the start of data collection, the marketing authorisation holder shall ensure that information on the study, including the study protocol, is notified to EMA. The marketing authorisation holder shall ensure that this information includes an English translation of the title and abstract of the study protocol.

6. The study protocol shall be amended and updated as needed throughout the course of the study. Any substantial amendment or update to the study protocol after the start of data collection shall be documented. The marketing authorisation holder shall ensure that the revised study protocol is submitted immediately to EMA.

7. The study protocol shall follow the format included in point 2 of this annex.

8. Within 12 months of the end of data collection, the marketing authorisation holder shall submit the final study report including a public abstract to EMA. The marketing authorisation holder shall ensure that an English translation of the abstract of the final study report is submitted.

9. The abstract of the final study report shall include a summary of the study methods and findings and shall follow the format included in point 3 of this annex.

10. The final study report shall follow the format included in point 4 of this annex.

11. EMA may publish appropriate templates for the protocol, abstract and final study report.

2. 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: Name and address of the marketing authorisation holder.

3. Responsible parties: Names, titles, qualifications, addresses, and affiliations of all responsible parties, including the main author of the protocol, the principal investigator, co-investigators, and a list of all collaborating primary institutions and other relevant study sites, clearly indicating the countries in which the study is to be performed.

4. Abstract: Stand-alone summary of the study protocol including the following sub-sections:

- Title with subtitles including version and date of the protocol and name and affiliation of main author
- Rationale and background
- Research question and objectives
- Study design
- Population
- Variables
- Data sources
- Study size
- Data analysis
- Milestones

5. Amendments and updates: Any substantial amendment and update to the study protocol after the start of data collection, including a justification for each amendment or update, dates of each 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:

- Start of data collection
- End of data collection
- Study progress report(s) requested pursuant to Art. 107m(5) of Directive 2010/84/EC
- Interim report(s) of study results, if applicable
- Final report of study results.

Timelines for important steps of the study conduct should be presented.

7. Rationale and background: Description of the safety hazard(s), the safety profile or the risk management measures that led to the initiation of the study, and critical review of all available published and unpublished data evaluating pertinent information and gaps in knowledge that the study is intended to fill. The review may encompass relevant animal and human

experiments, clinical studies, vital statistics and previous epidemiologic studies. The review should cite the findings of similar studies, and the expected contribution of the current study.

8. Research question and objectives: Research question that explains how the study will address the issue which led to the study being initiated, and research objectives, including any pre-specified hypotheses and main summary measures, describing the knowledge or information to be gained from the study.

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

9.1. Study design: Overall research design and rationale for this choice.

9.2. Setting: Study population defined in terms of persons, place, time period, and selection criteria. The rationale for any inclusion and exclusion criteria and their impact on the number of subjects available for analysis should be described. If any sampling from a source population is undertaken, description of the source population and details of sampling methods should be provided. In case where the study design is a systematic review or a meta-analysis, criteria for the selection and eligibility of studies should be explained.

9.3. Variables: Outcomes, exposures and other variables including measured risk factors, selection criteria, potential confounding variables and effect modifiers, including operational definitions.

9.4. Data sources: Strategies and data sources for determining exposures, outcomes and all other variables relevant to the study objectives, such as potential confounding variables and effect modifiers. Whenever validated data source, instruments and measures are used, the validation method should be described. If data collection methods or instruments are tested in a pilot study, plans for the pilot study should be presented. Any expert committees and evaluation procedures to be used to validate diagnosis should be described. Whenever 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 should be reported. In case of a systematic review or meta-analysis, the search strategy and processes and any methods for confirming data from investigators should be described.

9.5. Study size: Any projected study size, precision sought for study estimates and any calculation of the sample size that can minimally detect a pre-specified risk with a pre-specified power.

9.6. Data management: Data management and statistical software programs and hardware to be used in the study. Procedures for data collection, retrieval, collection and preparation.

9.7. Data analysis: All the major steps that lead from raw data to a final result, including methods used to correct inconsistencies or errors, impute values, modify raw data, categorise, analyse and present results, and procedures to control sources of bias and their influence on results; any statistical procedures to be applied to the data to obtain point estimates and confidence intervals of measures of occurrence or association and any sensitivity analysis.

9.8. Quality control: Description of any mechanisms and procedures to ensure data quality and integrity, including accuracy and legibility of collected data and original documents, storage of records and archiving of statistical programmes; description of available data on validity of recording and coding of any electronic data source used in the study, extent of source data verification and validation of endpoints. As appropriate, certification and/or qualifications of any supporting laboratory or research groups should be included.

9.9. Limitations of the research methods: Any potential limitations of the study design, data sources, and analytic methods, including issues relating to confounding, bias, generalisability, and random error. The likely success of efforts taken to reduce errors should be discussed.

10. Protection of human subjects: Information about whether study subjects will be placed at risk as a result of the study, provisions for maintaining confidentiality of information on study subjects, and potential circumstances and safeguards under which identifiable personal information may be provided to entities outside the study; consideration of the need for submitting the protocol to an Institutional Review Board/Independent Ethics Committee and the requirement of informed consent in accordance with local law.

11. Management and reporting of adverse events/adverse reactions: Procedures for collecting, management and reporting of individual cases of adverse events or adverse reactions. For certain study designs such as case-control or retrospective cohort studies, particularly those involving electronic health care records, systematic reviews and meta-analyses where it is not feasible to make a causality assessment at the individual case level, this should be stated.

12. Plans for disseminating and communicating study results

13. Resources required to conduct the study: Time, personnel, services (e.g. database access), and equipment required to conduct the study, including a brief description of the role of each of the personnel assigned to the research project.

14. References

15. Annexes: Any additional or complementary information on specific aspects not previously addressed (e.g. questionnaires, case report forms).

3. 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

7. Subjects and study size

8. Variables and data sources

9. Results

10. Discussion (including, if relevant, an evaluation of the impact of study results on the risk-benefit of the product)

11. Marketing Authorisation Holder

12. Name(s) and affiliation(s) of principal investigator(s)

4. 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 main author.

2. Abstract: Stand-alone summary in accordance with point 3 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 coinvestigators, and list of all collaborating primary institutions and other relevant study sites.

5. Milestones: Planned and actual dates for the following milestones:

- Start of data collection
- End of data collection
- Study progress report(s) requested pursuant to Art. 107m(5) of Directive 2001/83/EC
- Interim report(s) of study results, if applicable
- Final report of study results
- Any other important milestone applicable to the study, including date of protocol approval by an Institutional Review Board/Independent Ethics Committee if applicable, and date of study registration in the electronic study register.

6. Rationale and background: Description of the safety concern(s) that led to the study being initiated, and critical review of all available published and unpublished data evaluating pertinent information and gaps in knowledge that the study is intended to fill.

7. Research question and objectives: Research question and the research objectives, including any pre-specified hypotheses, as stated in the study protocol.

8. Amendments and updates to the protocol: List of any substantial amendment and update 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 the rationale for this choice.

9.2. Setting: Setting, locations, and relevant dates for the study, including periods of recruitment, follow-up, and data collection. In 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 of study subjects. Sources and methods of selection of participants should be provided, including, where relevant methods for case ascertainment.

9.4. Variables: All outcomes, exposures, predictors, potential confounders, and effect modifiers, including operational definitions. Diagnostic criteria are provided, if applicable.

9.5. Data sources and measurement: For each variable of interest, sources of data and details of methods of assessment and measurement (if applicable); comparability of assessment methods if there is more than one. 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 should be reported. In 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: Any efforts to assess and address potential sources of bias.

9.7. Study size: Study size, rationale for any sample 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:

- main summary measures
- all statistical methods applied to the study, including those used to control for confounding and, for meta-analyses, methods for combining results of studies
- any methods used to examine subgroups and interactions
- how missing data were addressed
- any sensitivity analyses
- any amendment to the plan of data analysis included in the study protocol, with a rationale for the change.

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

10. Results: Presentation of tables, graphs, and illustrations to present the pertinent data and reflect the analyses performed. Both unadjusted and adjusted results should be presented. Precision of estimates should be quantified using confidence intervals.

This section shall include the following sub-sections:

10.1. Participants: Numbers of individuals at each stage of study, e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed, and reasons for non-participation at any stage. In 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 for each variable of interest. In case of a systematic review or meta-analysis, characteristics of each study from which data were extracted (e.g. study size, follow-up).

10.3. Outcome data: Numbers of participants across categories of main outcomes, e.g. exposure or outcome.

10.4. Main results: Unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). If relevant, estimates of relative risk should be translated into absolute risk for a meaningful time period.

10.5. Other analyses: Other analyses done, e.g. analyses of subgroups and interactions, and sensitivity analyses.

10.6. Adverse events/ adverse reactions: Management and reporting of adverse events/adverse reactions. For certain study designs such as case-control or retrospective cohort studies, particularly those involving electronic health care records, systematic reviews and meta-analyses where it is not feasible to make a causality assessment at the individual case level, this should be stated.

11. Discussion

11.1. Key results: Key results with reference to the study objectives, prior research in support of and in contrast to present findings, and, if 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 (e.g., response rates, missing or incomplete data, imputations applied), sources of potential bias and imprecision and validation of the events. Both direction and magnitude of potential biases should 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: The generalisability (external validity) of the study results.

12. References.

13. Other information: Any additional or complementary information on specific aspects not previously addressed.

Consultation item no. 17: Do you agree with the proposed format? Please comment.

* * *