1 20 February 2012
2 EMA/813938/2011

3 Guideline on good pharmacovigilance practices (GVP)

4 Module VIII – Post-authorisation safety studies

Draft finalised by the Agency in collaboration with Member States and submitted to ERMS FG	19 January 2012
Draft agreed by ERMS FG	24 January 2012
Draft adopted by Executive Director	20 February 2012
Start of public consultation	21 February 2012
End of consultation (deadline for comments)	18 April 2012
Anticipated date for coming into effect after finalisation	July 2012

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Comments should be provided using this template. The completed comments form should be sent to gvp@ema.europa.eu.

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VIII.A. Introduction

A post-authorisation safety study (PASS) is defined as any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures [DIR Art 1(15)].

A PASS may be initiated, managed or financed by a marketing authorisation holder voluntarily, or pursuant to an obligation imposed by a competent authority as a condition to the granting of a marketing authorisation [REG Art 10(1), DIR Art 21a] or after the granting of a marketing authorisation if there are concerns about the risks of the authorised medicinal product [REG Art 10a, DIR Art 22a].

A PASS may be a clinical trial or a non-interventional study.

A PASS is non-interventional if the following requirements are cumulatively fulfilled (Volume 10 of The Rules Governing Medicinal Products in the European Union, Questions and Answers, Version 9.0, August 2011, Question 1.9)[1]:

- the medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorisation;
- the assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study; and
- no additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data.

Non-interventional studies are defined by the methodological approach used and not by the scientific objectives. Non-interventional studies include database research or review of records where all the events of interest have already happened (e.g. case-control, cross-sectional and cohort studies). Non-interventional studies also include those involving primary data collection (e.g. prospective observational studies and registries in which the data collected derive from routine clinical care), provided that the conditions set out above are met.

In this context, interviews, questionnaires and blood samples may be performed as part of normal clinical practice.

If a PASS is a clinical trial, the provisions of the following texts shall be followed:

- Directive 2001/20/EC provides legal obligations relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use;
- Volume 10 of The Rules Governing Medicinal Products in the European Union[1] contains detailed guidance documents applying to clinical trials.

The purposes of this Module are to:

- provide general guidance and requirements (according to Article 107m of Directive 2001/83/EC) for the conduct of any non-interventional PASS conducted by marketing authorisation holders, whether voluntarily or pursuant to obligations imposed by a competent authority (VIII.B.);
- provide general guidance and requirements for the protocol oversight and reporting and transparency of results of any non-interventional PASS conducted by marketing authorisation

[1] http://ec.europa.eu/health/documents/eudralex/vol-10/

holders pursuant to obligations imposed by a competent authority (including those listed in the risk management plan);

- provide general guidance and recommendations for the protocol and results transparency of any non-interventional PASS conducted voluntarily by marketing authorisation holders;
- describe the procedure whereby competent authorities may impose an interventional or non-interventional PASS to a marketing authorisation holder as an obligation in accordance with Articles 10 and 10a of Regulation (EC) No 726/2004 and Articles 21a and 22a of Directive 2001/83/EC, and describe the specific requirements (according to Articles 107n to 107q of Directive 2001/83/EC and Annex IV of the Commission Implementing Regulation on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC) that apply to non-interventional PASS conducted by marketing authorisation holders pursuant to such obligation (VIII.C.).

In this Module, all applicable legal requirements are referenced in the way explained in the GVP Introductory Cover Note and are usually identifiable by the modal verb "shall". Guidance for the implementation of legal requirements is provided using the modal verb "should".

VIII.B. Structures and processes

VIII.B.1. Scope

The guidance and requirements in section VIII.B. apply to non-interventional PASS which are initiated, managed or financed by the marketing authorisation holder within the European Union (EU), voluntarily or pursuant to obligations imposed in accordance with Articles 10 or 10a of Regulation (EC) No 726/2004 or with Articles 21a or 22a of Directive 2001/83/EC, and which involve the collection of data from patients and health care professionals [DIR Art 107m(1)]. These studies include those that make secondary use of data previously collected for another purpose and stored in medical or other (electronic) records.

Where relevant, a distinction is made between situations where the guidance represents an obligation and where it represents a recommendation.

These guidance and requirements should also be considered by marketing authorisation holders for studies developed and conducted outside the EU.

VIII.B.2. Definitions

Date at which a study commences: date of the start of data collection.

Start of data collection: the date from which information on the first study patient is first recorded in the study dataset, or, in case of secondary use of data, the date on which the data extraction starts. [IM Annex IV.1(2)].

End of data collection: the date on which the analytical dataset is first completely available. [IM Annex IV.1(3)].

Substantial amendment to the study protocol: amendment to the protocol that is likely to have an impact on the safety, physical or mental well-being of the study participants or may affect the study results and their interpretation, such as changes to the primary or secondary objectives of the study, to the study population, to the sample size, to the definitions of the main exposure, outcome and confounding variables and to the analytical plan.

VIII.B.3. General principles

The primary purpose of non-interventional PASS should be to generate scientific data of potential clinical or public health importance. Such studies shall not be performed where the act of conducting the study promotes the use of a medicinal product [DIR Art 107m(3)].

Objectives of a non-interventional PASS (and, more generally of any PASS, whether interventional or non-interventional PASS) may include:

- to characterise the safety profile of a medicine (e.g. to identify the most frequent adverse reactions occurring in a large population over time);
- to provide reassurance about the absence of a safety concern related to a specific adverse reaction;
- to investigate potential or identified risks, e.g. to characterise the incidence rate, estimate the rate ratio or rate difference in comparison to a non-exposed population and investigate risk factors and effect modifiers;
- to evaluate risks of a medicinal product used in authorised indications by patient groups not studied in the pre-authorisation phase (e.g. pregnant women, elderly patients);
- to assess patterns of drug utilisation and use of the medicinal product that may have an impact on its safety (e.g. co-medication, medication errors);
- to evaluate the effectiveness of a risk minimisation activity (e.g. drug utilisation study, patient or physician survey).

Relevant scientific guidance should be considered by marketing authorisation holders and investigators for the development of study protocols, the conduct of studies and the writing of study reports and, where applicable, by the Pharmacovigilance Risk Assessment Committee (PRAC) and national competent authorities for the evaluation of study protocols and study reports. Relevant scientific guidance includes the ENCePP Guide on Methodological Standards in Pharmacoepidemiology[2], the ENCePP Checklist for Study Protocols[3] and the Guidelines for Good Pharmacoepidemiology Practices of the International Society of Pharmacoepidemiology (ISPE GPP, Revision 2, 2007)[4]. Procedures should be in place to ensure full transparency of relevant information pertaining to the study, including publication of the final results.

For studies that are funded by a marketing authorisation holder and are developed, conducted or analysed fully or partially by investigators who are not employees of the marketing authorisation holder, the marketing authorisation holder should ensure that the investigators are qualified by education, training and experience to perform their tasks. A research contract between the marketing authorisation holder and investigators may ensure that the study meets its regulatory requirements while permitting their scientific expertise to be exercised throughout the research process. It is recommended that the research contract takes into account the provisions of the ENCePP Code of Conduct[5] and addresses the following aspects:

- rationale, main objectives and brief description of the intended methods of the research to be carried out by the external investigator(s);
- rights and obligations of the investigator(s) and marketing authorisation holder;

[2] http://www.encepp.eu/standards_and_guidances/documents/ENCePPGuideofMethStandardsinPE.pdf
[3] http://www.encepp.eu/standards_and_guidances/documents/ENCePPChecklistforStudyProtocols.doc
[4] http://www.pharmacoepi.org/resources/guidelines_08027.cfm
[5] http://www.encepp.eu/code_of_conduct/index.html

- clear assignment of tasks and responsibilities;
- procedure for achieving agreement on the study protocol;
- provisions for meeting the marketing authorisation holder's pharmacovigilance obligations, including the reporting of serious adverse reactions and other safety data by investigators, if applicable;
- intellectual property rights arising from the study and access to study data;
- storage and availability of analytical dataset and statistical programmes for audit and inspection;
- communication strategy for the scheduled progress and final reports;
- publication strategy of interim and final results.

Payments to healthcare professionals for participating in non-interventional post-authorisation safety studies shall be restricted to compensation for time and expenses incurred [DIR Art 107m(4)].

VIII.B.4. Study protocol

All post-authorisation safety studies must have a written study protocol before the study commences. The study should follow a scientifically sound protocol developed by individuals with appropriate scientific background and experience. EU and, where present, national requirements shall be followed for ensuring the well-being and rights of the participants [DIR Art 107m(2)].

For PASS voluntarily initiated by the marketing authorisation holder, the marketing authorisation holder is encouraged to transmit the study protocol prior to the start of data collection to the national competent authority of the Member States where the product is authorised and to the Agency for PASS concerning products authorised pursuant to Regulation (EC) No 726/2004. The marketing authorisation holder may be required by the national competent authority to submit the protocol to the competent authorities of the Member States in which the study is conducted [DIR Art 107m(5)].

For PASS initiated by the marketing authorisation holder pursuant to an obligation imposed in accordance with Articles 10 or 10a of Regulation (EC) No 726/2004 or with Articles 21a or 22a of Directive 2001/83/EC, see VIII.C.4.2.. Prior to the start of data collection, the marketing authorisation holder must ensure that information on the study, including the study protocol, is notified to the Agency or the national competent authority, as applicable, and that the Member State in which the study is conducted is informed. That information shall include an English translation of the title and abstract of the study protocol [IM Annex IV.1(4)].

In order to ensure compliance of the marketing authorisation holder with its pharmacovigilance obligations, the qualified person responsible for pharmacovigilance (QPPV) (see Module I) should be involved in the review and sign-off of study protocols. Where applicable, the contact person for pharmacovigilance at national level should be informed of any study conducted in that Member State and receive a copy of the protocol.

The marketing authorisation holder is encouraged to make the study protocol publicly available in the register of non-interventional post-authorisation safety studies maintained by the Agency before the start of data collection. Where prior publication of the protocol could threaten the validity of the study (for example, in a case-control study where prior knowledge of the exposure of interest could lead to information bias) or the protection of intellectual rights, an amended study protocol may be made available in the register prior to the start of data collection, with the appropriate amendments or redactions. These should be justified and kept to the minimum necessary for the objective aimed by the redaction process. Whenever an amended study protocol is published prior to the start of data

collection, the complete study protocol should be made available in the register at the end of data collection.

VIII.B.4.1. Format and content of the study protocol

The study protocol should follow the following format:

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, all 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; see VIII.B.1. for the definition of a substantial amendment to the study protocol.
6. **Milestones**: table with planned dates for the following milestones:
    - Start of data collection
    - End of data collection
    - Study progress report(s) requested under Article 107m(5) of Directive 2001/83/EC
    - Interim report(s) of study results, if applicable
    - Final report of study results

Any other important timelines in 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. Where the study design is a systematic review or a meta-analysis, the criteria for the selection and eligibility of studies should be explained.

    9.3. **Variables**: outcomes, exposures and other variables including measured risk factors, 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 sources, 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 diagnoses 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**: safeguards in order to comply with national and EU 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**: procedures for the collection, management and reporting of individual cases of adverse reactions and of any new information that might influence the evaluation of the benefit-risk balance of the product while the study is being conducted. For certain study designs where expedited reporting is not required (see Module VI), this should be stated in the protocol.

12. **Plans for disseminating and communicating study results** including plans for submission of progress reports, final reports and publications.

13. **References.**

It is recommended that Annexes include the ENCePP Checklist for Study Protocols signed by the principal investigator. They may also include any additional or complementary information on specific aspects not previously addressed (e.g. questionnaires, case report forms).

Feasibility studies that were carried out to support the development of the protocol, for example, the testing of a questionnaire or simple counts of medical events or prescriptions in a database to determine the statistical precision of the study, should be reported in the appropriate section of the study protocol, with a brief description of their methods and results. Feasibility studies that are part of the research process should be fully described in the protocol, for example, a pilot evaluation of the study questionnaire(s) used for the first set of patients recruited into the study.

VIII.B.4.2. Change control of the study protocol

The study protocol should be amended and updated as needed throughout the course of the study. Any substantial changes to the protocol after the study start should be documented in the protocol in a traceable and auditable way including the dates of the changes. If changes to the protocol lead to the study being considered an interventional clinical trial, the study shall subsequently be conducted in accordance with Directive 2001/20/EC and Volume 10 of The Rules Governing Medicinal Products in the European Union.

For PASS voluntarily initiated by the marketing authorisation holder, the marketing authorisation holder is encouraged to transmit the updated protocol to the national competent authority of the Member States where the product is authorised, and to the Agency for PASS concerning products authorised pursuant to Regulation (EC) No 726/2004.

For PASS initiated by the marketing authorisation holder pursuant to an obligation imposed in accordance with Articles 10 and 10a of Regulation (EC) No 726/2004 and with Articles 21a and 22a of Directive 2001/83/EC, see VIII.C.4.2.. The study protocol shall be amended as needed throughout the course of study and any substantial amendments to the protocol shall be submitted before their implementation [IM Annex IV.1(4)].

The marketing authorisation holder is encouraged to have updated study protocols entered in the register of non-interventional post-authorisation safety studies maintained by the Agency.

VIII.B.5. Reporting of pharmacovigilance data to competent authorities

VIII.B.5.1. Data relevant to the risk-benefit balance of the product

The marketing authorisation holder shall monitor the data generated while the study is being conducted and consider their implications for the risk-benefit balance of the medicinal product concerned [DIR Art 107m(7)]. Any new information that might influence the evaluation of the risk-benefit balance of the medicinal product shall immediately be communicated to competent authorities of the Member States in which the product is authorised and additionally to the Agency for products authorised pursuant to Regulation (EC) No 726/2004 [DIR Art 23, Art 107m(7), REG Art 16]. Such information affecting the benefit-risk balance of the medicinal product may include that arising from a review of suspected adverse reactions or an interim analysis of aggregated safety data.

This communication should not affect information on the results of studies which should be provided by means of periodic safety update reports (PSURs) (see Module VII) and in risk management plan (RMP) updates (see Module V), where applicable.

VIII.B.5.2. Suspected adverse reactions to be reported in an expedited manner

Procedures for the collection, management (including a review by the marketing authorisation holder if appropriate) and expedited reporting of suspected adverse reactions in accordance to the provisions of Module VI should be put in place and described in the study protocol. For study designs where expedited reporting is not required (see Module VI), this should be stated in the study protocol.

VIII.B.5.3. Study reports

VIII.B.5.3.1. Progress reports

Progress reports may be requested by a national competent authority [DIR Art 107m(5)]. They may also be requested by the PRAC and by the Agency for PASS concerning products authorised pursuant to Regulation (EC) No 726/2004. Requests for progress reports may be made before the study commences or any time during the study conduct. They may be guided by the communication of benefit-risk information arising from the study or the need for information about the study progress in the context of regulatory procedures or important safety communication about the product.

Upon request from a national competent authority, progress reports shall be submitted to the competent authorities of the Member States in which the study is conducted [DIR Art 107m(5)].

The timing of the progress reports should be agreed with the relevant competent authorities and specified in the study protocol. Study progress should also be reported in any periodic safety update reports (PSURs) (see Module VII) and risk management plan (RMP) updates (see Module V), where applicable.

The content of the progress report should follow a logical sequence and should include all the available data that is judged relevant for the progress of the study, for example, number of patients who have entered the study, number of exposed patients or number of patients presenting the outcome, problems encountered and deviations from the expected plan. After review of the report, additional information may be requested.

VIII.B.5.3.2. Final study report

The study report should be submitted to the competent authority(ies) as soon as possible after its finalisation and within 12 months of the end of data collection. The marketing authorisation holder shall submit the final study report to competent authorities of the Member States in which the study was conducted [DIR Art 107m(6)].

For PASS voluntarily initiated by the marketing authorisation holder, the marketing authorisation holder is also encouraged to transmit the final study report to the national competent authority of the Member States where the product is authorised, and to the Agency for PASS concerning products authorised pursuant to Regulation (EC) No 726/2004.

For PASS initiated by the marketing authorisation holder pursuant to an obligation imposed in accordance with Articles 10 or 10a of Regulation (EC) No 726/2004 or with Articles 21a or 22a of Directive 2001/83/EC, see VIII.C.4.2.. Unless a waiver has been granted, the marketing authorisation holder shall, within 12 months of the end of data collection, submit the final study report, including a public abstract, to the Agency and the national competent authority, as applicable. The marketing authorisation holder shall ensure that an English translation of the abstract is submitted [IM Annex IV.1(5)].

If a study is discontinued, a final report should be submitted and the reasons for terminating the study should be provided.

The final study report should follow the following format:

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 the format presented below.
3. **Marketing authorisation holder**: name and address of the marketing authorisation holder.
4. **Investigators**: names, titles, degrees, addresses and affiliations of all investigators, 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 DIR Art 107m(5)
    - 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, 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 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), and 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 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 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.

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.

The abstract of the final study report should include a summary of the study methods and findings presented in the following format:

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).

The marketing authorisation holder is encouraged to have the final study report entered in the register of non-interventional post-authorisation safety studies maintained by the Agency, including an English translation of the abstract.

VIII.B.6. Publication of study results by investigators

For studies that are fully or partially conducted by investigators who are not employees of the marketing authorisation holder, the marketing authorisation is encouraged to agree in advance a publication strategy with the principal investigator. It is recommended that this strategy allows the principal investigator to independently prepare publications based on the study results irrespective of data ownership. In this case, the marketing authorisation holder should be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication, while avoiding unjustifiable delays of the publication. Requests for changes to the manuscript should be based on sound scientific reasons. The marketing authorisation holder should be allowed to require deletion of confidential information.

VIII.B.6.1. Submission of published study results to competent authorities

The marketing authorisation holder is encouraged to transmit the final manuscript of the article to the Agency and the competent authorities of the Member States in which the product is authorised within two weeks after acceptance of the publication.

VIII.B.7. Data protection

Marketing authorisation holders and investigators shall follow relevant national legislation and guidance of those Member States where the study is being conducted [DIR Art 107m(2)]. The legislation on data protection must be followed in accordance with Directive 95/46/EC of the European Parliament and of the Council on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

The marketing authorisation holder should ensure that all study information is handled and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of the records of the study subjects remains protected [IM Annex IV.1(6) for PASS initiated by the marketing authorisation holder pursuant to an obligation imposed in accordance with Articles 10 and 10a of Regulation (EC) No 726/2004 and Articles 21a and 22a of Directive 2001/83/EC].

VIII.B.8. Quality systems, audits and inspections

The marketing authorisation holder should ensure the fulfilment of its pharmacovigilance obligations in relation to the study and that this can be audited, inspected and verified. Any change to the data should be documented to enable traceability. When the study makes secondary use of data from electronic records, verification of records refers to the analytical dataset. The marketing authorisation holder should 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 [IM Annex IV.1(6) for PASS initiated by the marketing authorisation holder pursuant to an obligation imposed in accordance with Articles 10 and 10a of Regulation (EC) No 726/2004 and Articles 21a and 22a of Directive 2001/83/EC].

VIII.B.9. Study registration

The marketing authorisation holder is encouraged to have information on the study, including the study protocol, entered prior to the start of data collection into the electronic register of non-interventional post-authorisation safety studies maintained by the Agency. This information should include an English translation of the title of the study and of the abstract of the study protocol. In case of substantial amendments to the study protocol, the marketing authorisation holder is encouraged to have the revised study protocol entered into the electronic study register (see also VIII.B.4. for cases where publication of the protocol could threaten the validity of the study or the protection of intellectual rights).

At the end of the study, the marketing authorisation holder is encouraged to have the final study report entered into the electronic study register, including an English translation of the abstract.

VIII.B.10. Impact on the risk management system

Non-interventional PASS (and, more generally, any interventional or non-interventional PASS, see Module V) conducted to investigate a safety concern, as described in a risk management plan (RMP), should be included in the RMP. The study protocol should be appended to the RMP (see Module V).

VIII.C. Operation of the EU network

VIII.C.1. Scope

The provisions of VIII.C. refer specifically to post-authorisation safety studies initiated, managed or financed by marketing authorisation holders pursuant to obligations imposed by a competent authority in accordance with Articles 10 and 10a of Regulation (EC) No 726/2004 and Articles 21a and 22a of Directive 2001/83/EC. Sections VIII.C.2. and VIII.C.3. apply to both interventional and non-interventional PASS. Sections VIII.C.4. to VIII.C.7. apply to non-interventional PASS.

VIII.C.2. Procedure for imposing post-authorisation safety studies

In the EU, the conduct of a post-authorisation safety study (PASS) can be imposed during the evaluation of the initial marketing authorisation application or during the post-authorisation phase whenever there are concerns about the risks of an authorised medicinal product. This obligation shall be duly justified based on benefit-risk considerations, shall be notified in writing and shall include the objectives and timeframe for the submission and conduct of the study [DIR Art 22a, REG Art 10a]. The request may also recommend key elements of the study (e.g. study design, setting, exposure(s),

outcome(s), population to be addressed). An overview of study designs and databases frequently used in post-authorisation safety studies is provided in VIII.Appendix 1. at the end of this Module.

a. Request of a post-authorisation safety study as part of the initial marketing authorisation application

A marketing authorisation may be granted subject to the conduct of a PASS [DIR Art 21a, REG Art 10]. If the need for a PASS is identified for a centrally authorised product or a nationally authorised product authorised through the mutual recognition or the decentralised procedure, the PRAC will adopt a recommendation to the Committee for Medicinal Products for Human Use (CHMP) or to the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) as applicable.

b. Request for a post-authorisation safety study during a post-authorisation regulatory procedure

The need for a PASS could be identified during a post-authorisation regulatory procedure, for example, an extension or a variation to a marketing authorisation or a renewal procedure. If the need for a PASS is identified for a centrally authorised product or a nationally authorised product through the mutual recognition or the decentralised procedure, the PRAC will adopt a recommendation to the CHMP or the CMDh as applicable.

c. Request for a post-authorisation safety study due to an emerging safety concern

After the granting of the marketing authorisation, the Agency or a national competent authority, where applicable, may impose on the marketing authorisation holder an obligation to conduct a post-authorisation safety study if there are concerns about the risk of the authorised medicinal product [DIR Art 22a, REG Art 10a], for example following evaluation of a safety signal (see Module IX).

If safety concerns apply to more than one medicinal product, the national competent authority or the Agency shall, following consultation with the PRAC, encourage the marketing authorisation holders concerned to conduct a joint PASS [DIR Art 22a, REG Art 10a]. Requests to the marketing authorisation holders should contain the elements of the study design that support the joint proposal. Upon request from the marketing authorisation holders, the national competent authority or the Agency may organise a pre-submission meeting in order to provide suggestions for a joint proposal and facilitate agreement in developing a joint protocol. If a joint protocol is not voluntarily agreed and different proposals are submitted, the national competent authority or Agency may adopt, in consultation with the PRAC, the key elements (for example, the study design and the definition of exposure and outcomes) which each marketing authorisation holder should include in the study protocol. These key elements may then be imposed on all the marketing authorisation holders, pursuant to Article 22a of Directive 2001/83/EC or Article 10a of Regulation (EC) No 726/2004. The study protocols should be implemented within a timescale laid down by the national competent authority or the Agency in consultation with the PRAC and imposed according to Article 22a of Directive 2001/83/EC or Article 10a of Regulation (EC) No 726/2004.

Within 30 days of receipt of the written notification of the obligation, the marketing authorisation holder may request the opportunity to present written observations in response to the imposition of the obligation [DIR Art 22a(2), REG Art 10a(2)]. The national competent authority or the Agency shall specify a time limit for the provision of these observations. On the basis of the written observations submitted by the marketing authorisation holder, the national competent authority, the Agency or the European Commission shall withdraw or confirm the obligation. When the obligation is confirmed, the marketing authorisation shall be subject to variation to include the obligation as a condition and the risk management plan (RMP), where applicable, shall be updated accordingly [DIR Art 22a(3), REG Art 10a(3)] (see Module V and VIII.C.3.).

VIII.C.3. Impact of a post-authorisation safety study on the risk management system

All post-authorisation safety studies imposed as a condition to the marketing authorisation will be described in the RMP (see Module V) and their results provided in the next PSUR (see Module VI), where applicable.

When a RMP does not exist, a new RMP should be developed referring to the post-authorisation safety study. All relevant sections/modules of the RMP should be amended to document the conduct of the study, including the safety specification, the pharmacovigilance plan, the risk minimisation plan and the summary of activities, as appropriate. A copy of the study protocol approved by the competent authority should be provided in the relevant annex.

Should the results of the post-authorisation safety study require a variation to the marketing authorisation, an updated RMP should be submitted to the Agency or to the relevant national competent authorities as applicable, together with a variation.

VIII.C.4. Supervision of non-interventional post-authorisation safety studies

VIII.C.4.1. Roles and responsibilities of the marketing authorisation holder

The marketing authorisation holder has the responsibility to ensure that the study is not a clinical trial, in which case Directive 2001/20/EC shall apply. If the study is a non-interventional study (see VIII.A.), the marketing authorisation holder shall ensure that the study meets the requirements applicable to non-interventional PASS set out in Articles 107m to 107q of Directive 2001/83/EC, in Annex IV of the Commission Implementing Regulation on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC and in VIII.B. as well as the requirements specific to the requested PASS. The marketing authorisation holder shall ensure the fulfilment of its pharmacovigilance obligations in relation to the study and that this can be audited, inspected and verified [IM Annex IV.1(6)] (see VIII.B.7. and VIII.B.8.).

VIII.C.4.2. Regulatory oversight

Non-interventional PASS conducted pursuant to obligations imposed by a competent authority are supervised and assessed by the PRAC, unless the PASS was requested by a national competent authority of a single Member State according to article 22a of Directive 2001/83/EC and conducted only in that Member State, in which case national oversight procedures apply [DIR Art 107n(1)].

Following the imposing of the obligation to conduct a non-interventional PASS, the marketing authorisation holder shall develop a study protocol and submit it to the national competent authority or the PRAC for review [DIR Art 107n(1)]. The study protocol shall follow the format of IM Annex IV.1(4) and 2(1-13) and should consider additional specifications set out in VIII.B.4.1..

In case the PRAC is involved in the oversight of the study, the PRAC will nominate a PRAC rapporteur responsible for the supervision of the PASS. Prior to submission of the protocol, the marketing authorisation holder may submit a request to the Agency for a pre-submission meeting with the Agency and the PRAC rapporteur in order to clarify specific aspects of the requested study (such as study objectives, study population, definition of exposure and outcomes) and to facilitate the development of the protocol in accordance with the objectives determined by the PRAC. Any pre-submission meeting will not impact on the imposed timelines. The marketing authorisation holder shall submit the study protocol to the Agency and to the PRAC. The Agency will provide the PRAC rapporteur

with a summary of the study protocol. The PRAC rapporteur should write a protocol assessment report, including a list of questions if appropriate, and submit it for review and approval by the PRAC. If the study proves to be interventional, the PRAC rapporteur should not provide an assessment report but should issue an explanatory statement to the marketing authorisation holder that the study is a clinical trial falling under the scope of Directive 2001/20/EC.

Within 60 days from submission of the draft protocol, the national competent authority or the PRAC shall issue a letter endorsing the draft protocol, a letter of objection or a letter notifying the marketing authorisation holder that the study is a clinical trial falling under the scope of Directive 2001/20/EC. The letter of objection shall set out in detail the grounds for the objection in any of the following cases:

- it is considered that the conduct of the study promotes the use of a medicinal product; and
- it is considered that the design of the study does not fulfil the study objectives [DIR Art 107n(2)].

The study may commence only when the written endorsement from the national competent authority or the PRAC, as appropriate as been issued [DIR Art 107n(3)]. In cases where the letter of endorsement has been issued by the PRAC, the marketing authorisation holder should forward the protocol to the competent authority of the Member State(s) in which the study is to be conducted. The study may start only on receipt of the letter of endorsement by the PRAC and only after the relevant national competent authority(ies) have received a copy of the PRAC endorsed protocol [DIR Art 107n(3)]. EU and national requirements shall be followed to ensure the well-being and rights of participants in the study [DIR Art 107m(2)].

After a study has been commenced, any substantial amendments to the protocol shall be submitted, before their implementation, to the national competent authority or to the PRAC, as appropriate (see VIII.B.1. for the definition of a substantial amendment). The national competent authority or the PRAC, as appropriate, shall assess the amendments and inform the marketing authorisation holder of its endorsement or objection [DIR Art 107o]. In case of PRAC involvement, the marketing authorisation holder should submit the amended protocol to the Agency together with a letter of justification for the proposed amendment. This request will be evaluated by the PRAC and a letter of endorsement or objection will be provided to the marketing authorisation holder within 30 days of submission.

Upon completion of the study, the marketing authorisation holder shall submit a final study report, including a public abstract, to the national competent authority or to the PRAC as soon as possible and not later than 12 months after the end of data collection, unless a written waiver has been granted by the national competent authority or the PRAC, as appropriate [DIR Art 107p(1)]. The final study report shall follow the format of IM Annex IV.1(5) and 4(1-12), with consideration to the additional specifications set out in VIII.B.5.3.2.. The public abstract shall follow the format of IM Annex IV.1(5) and 3(1-12). An English translation of the abstract shall be provided.

In case of PRAC involvement, the marketing authorisation holder should request the waiver in writing to the Agency at least three months before the due date for the submission of the report. The request should be assessed by the PRAC rapporteur and granted or rejected by the PRAC on the basis of the justification and timeline submitted by the marketing authorisation holder. The Agency will inform the marketing authorisation holder in writing of the decision of the PRAC.

In cases where the PRAC has assessed the final study results, the Agency will provide the marketing authorisation holder with the PRAC assessment report, including a list of questions as appropriate. If the PRAC addresses a list of questions to the marketing authorisation holder, the PRAC conclusion on the study results, including their recommendations to the CHMP or CMDh , as applicable (see VIII.C.5.), will be decided once the marketing authorisation holder has addressed the questions posed.

VIII.C.5. Changes to the marketing authorisation following results from a non-interventional post-authorisation safety study

The marketing authorisation holder shall evaluate whether the results have an impact on the marketing authorisation and shall, if necessary, submit to the national competent authorities or the Agency an application to vary the marketing authorisation [DIR Art 107p(2)]. In such case, the variation should be submitted to the national competent authority or the Agency with the final study report within 12 months of the end of data collection. Where applicable, the PRAC and the CHMP or the CMDh will coordinate the assessment of the study results within the variation procedure.

Following the review of the final study report, the PRAC may recommend variation, suspension or revocation of the marketing authorisation [DIR Art 107q(2), REG Art 28b(2)]. The recommendation by the PRAC shall mention any divergent positions and the grounds on which they are based [DIR Art 107q(1)].

For centrally authorised products, or substances for which at least one centrally-authorised product exists, recommendations for the variation, suspension or revocation of the marketing authorisation made by the PRAC shall be transmitted to the CHMP which shall adopt an opinion taking into account the recommendation. The CHMP opinion shall be transmitted to the European Commission. The Commission shall adopt a decision in accordance with Article 10 of Regulation (EC) No 726/2004. When the opinion of the CHMP differs from the recommendation of the PRAC, the CHMP shall attach to its opinion a detailed explanation [REG Art 28b(2)].

For nationally authorised products including those authorised through the mutual recognition or the decentralised procedure and for substances where no centrally-authorised product exists, the Member States represented within the CMDh shall agree a position taking into account the PRAC recommendation and include a timetable for the implementation of this agreed position. When a consensus agreement is reached, the chairman of the CMDh shall record the agreement and send the agreed position to the marketing authorisation holder and Member States who should adopt necessary measures to vary, suspend or revoke the marketing authorisation in line with the implementation timetable of the CMDh. In case a variation is agreed upon, the marketing authorisation holder shall submit to the national competent authorities an appropriate application for a variation, including an updated summary of product characteristics (SmPC) and package leaflet within the determined timetable for implementation. In case a consensus agreement cannot be reached, the position of the majority of the Member States represented within the CMDh should be forwarded to the Commission who shall apply the procedure laid down in Articles 33 and 34 of Directive 2001/83/EC. Where the agreement reached by the Member States represented within the CMDh or the position of the majority of Member States differs from the recommendation of the PRAC, the CMDh shall attach to the agreement or majority position a detailed explanation of the scientific grounds for differences together with the recommendation [DIR Art 107q(2)].

More urgent action may be required in certain circumstances, for example, based on interim results included in progress reports (see also VIII.B.5.3.1.).

VIII.Appendix 1. Methods for post-authorisation safety studies[6]

VIII.App1.1. Study designs

Post-authorisation safety studies may adopt different designs depending on their objectives. A brief description of the fundamental types of studies, as well as the types of data resources available, is provided hereafter. However, this Appendix is not intended to be exhaustive and should be complemented with other widely available information sources [VIII.App 1. References 1-5].

VIII.App1.1.1. Active surveillance

Active surveillance, in contrast to passive surveillance, seeks to ascertain more completely the number of adverse events in a given population via a continuous organised process. An example of active surveillance is the follow-up of patients treated with a particular medicinal product through a risk management system. Patients who fill a prescription for this product may be asked to complete a brief survey form and give permission for later contact. In general, it is more feasible to get comprehensive data on individual adverse event reports through an active surveillance system than through a passive reporting system. Automatic detection of abnormal laboratory values from computerised laboratory reports in certain clinical settings may also provide an efficient active surveillance system.

VIII.App1.1.1.1. Sentinel sites

Active surveillance may be achieved by reviewing medical records or interviewing patients and/or physicians/pharmacists in a sample of sentinel sites to ensure complete and accurate data on reported adverse events. The selected sites may provide information, such as data from specific patient subgroups that would not be available in a passive spontaneous reporting system. Further, collection of information on the use of a medicinal product, such as the potential for abuse, may be targeted at selected sentinel sites. Some of the major weaknesses of sentinel sites are problems with selection bias, small numbers of patients, and increased costs. Active surveillance with sentinel sites is most efficient for those medicinal products used mainly in institutional settings such as hospitals, nursing homes, and haemodialysis centres. Institutional settings may have a greater frequency of use for certain products and may provide an infrastructure for dedicated reporting. In addition, automatic detection of abnormal laboratory values from computerised laboratory reports in certain clinical settings may provide an efficient active surveillance system.

VIII.App1.1.1.2. Intensive monitoring schemes

Intensive monitoring is a system of record collation in designated areas, e.g. hospital units or by specific healthcare professionals in community practice. In such cases, the data collection may be undertaken by monitors who attend ward rounds, where they gather information concerning undesirable or unintended events thought by the attending physician to be causally related to the medication. Monitoring may also be focused on certain major events that tend to be drug-related such as jaundice, renal failure, haematological disorders, bleeding. The major strength of such systems is that the monitors may document important information about the events and exposure to medicinal products. The major limitation is the need to maintain a trained monitoring team over time.

[6] See also the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which provides a methodological framework and a compilation of existing guidelines in the fields of pharmacoepidemiology and pharmacovigilance: http://www.encepp.eu/standards_and_guidances/documents/ENCePPGuideofMethStandardsinPE.pdf

VIII.App1.1.1.3. Prescription event monitoring

In prescription event monitoring, patients may be identified from electronic prescription data or automated health insurance claims. A follow-up questionnaire can then be sent to each prescribing physician or patient at pre-specified intervals to obtain outcome information. Information on patient demographics, indication for treatment, duration of therapy (including start dates), dosage, clinical events, and reasons for discontinuation can be included in the questionnaire [VIII.App 1. References 6-7]. Limitations of prescription event monitoring include incomplete physician response and limited scope to study products which are used exclusively in hospitals. More detailed information on adverse events from a large number of physicians and/or patients may be collected.

VIII.App1.1.1.4. Registries

A registry should be considered a structure within which studies can be performed, i.e. a data source, where entry is defined either by diagnosis of a disease (disease registry) or prescription of a drug (exposure registry)[7].

Disease/outcome registries, such as registries for blood dyscrasias, severe cutaneous reactions, or congenital malformations may help collect data on drug exposure and other factors associated with a clinical condition. A disease registry might also be used as a base for a case-control study comparing the drug exposure of cases identified from the registry and controls selected from either patients within the registry with another condition, or from outside the registry or a case-only design (see VIII.App 1.1.2.4.).

Exposure registries address populations exposed to medicinal products of interest (e.g. registry of rheumatoid arthritis patients exposed to biological therapies) to determine if a medicinal product has a special impact on this group of patients. Some exposure registries address exposures to medicinal products in specific populations, such as pregnant women. Patients may be followed over time and included in a cohort study to collect data on adverse events using standardised questionnaires. Simple cohort studies may measure incidence, but, without a comparison group, cannot evaluate any association between exposures and outcomes. Nonetheless, they may be useful for signal amplification particularly for rare outcomes. This type of registry may be very valuable when examining the safety of an orphan drug indicated for a specific condition.

VIII.App1.1.2. Observational studies

Traditional epidemiological methods are a key component in the evaluation of adverse events. There are a number of observational study designs that are useful in validating signals from spontaneous reports or case series. Major types of these designs are cross-sectional studies, case-control studies, and cohort studies (both retrospective and prospective).

VIII.App1.1.2.1. Cross-sectional study (survey)

Data collected on a population of patients at a single point in time (or interval of time) regardless of exposure or disease status constitute a cross-sectional study. These types of studies are primarily used to gather data for surveys or for ecological analyses. A drawback of cross-sectional studies is that the temporal relationship between exposure and outcome cannot be directly addressed, which limits its use for etiologic research unless the exposures do not change over time. These studies are best used to examine the prevalence of a disease at one time-point or to examine trends over time, when data for

[7] AHRQ Registries for Evaluating Patient Outcomes: A User's Guide. http://www.effectivehealthcare.ahrq.gov/ehc/products/74/531/Registries%202nd%20ed%20final%20to%20Eisenberg%209-15-10.pdf

serial time-points can be captured. These studies may also be used to examine the crude association between exposure and outcome in ecologic analyses.

VIII.App1.1.2.2. Cohort Study

In a cohort study, a population-at-risk for an event of interest is followed over time for the occurrence of that event. Information on exposure status is known throughout the follow-up period for each patient. A patient might be exposed to a medicinal product at one time during follow-up, but non-exposed at another time point. Since the population exposure during follow-up is known, incidence rates can be calculated. In many cohort studies involving exposure to medicinal product(s), comparison cohorts of interest are selected on the basis of medication use and followed over time. Cohort studies are useful when there is a need to know the incidence rates of adverse events in addition to the relative risks of adverse events. Multiple adverse events may also be investigated using the same data source in a cohort study. However, it may be difficult to recruit sufficient numbers of patients who are exposed to a product of interest (such as an orphan drug) or to study very rare outcomes. The identification of patients for cohort studies may come from large automated databases or from data collected specifically for the study at hand. In addition, cohort studies may be used to examine safety concerns in special populations (the elderly, children, patients with co-morbid conditions, pregnant women) through over-sampling of these patients or by stratifying the cohort if sufficient numbers of patients exist. Cohort studies may be prospective or retrospective depending on when the outcome of interest occurs in relation to the commencement of the research: If the outcome occurs after the research begins, it would be prospective; if the outcome had already occurred when the investigation began, it would be retrospective.

VIII.App1.1.2.3. Case-control study

In a case-control study, cases of disease (or events) are identified and patients without the disease or event of interest at the time of selection, are then selected as controls from the source population that gave rise to the cases. The exposure status of the two groups is then compared using the odds ratio, which is an estimate of the relative risk of disease among the exposed as compared to the non-exposed. Patients may be identified from an existing database or using data collected specifically for the purpose of the study of interest. If safety information is sought for special populations, the cases and controls may be stratified according to the population of interest (the elderly, children, pregnant women, etc.). Existing large population-based databases are a useful and efficient means of providing needed exposure and medical outcome data in a relatively short period of time. Case-control studies are particularly useful when the goal is to investigate whether there is an association between a medicinal product (or products) and one specific rare adverse event, as well as to identify risk factors for adverse events (or actually, effect-modifiers). Risk factors may include conditions such as renal and hepatic dysfunction, which might modify the relationship between the drug exposure and the adverse event. Under specific conditions, a case-control study may also provide the absolute incidence rate of the event. If all cases of interest (or a well-defined fraction of cases) in the catchment area are captured and the fraction of controls from the source population is known, an incidence rate can be calculated. As in cohort studies, case-control studies may be prospective or retrospective (see VIII.App 1.1.2.2.).

When the source population within which the case-control study is conducted is a well-defined cohort, it is then possible to select a random sample from it to form the control series. The name “nested case-control study” has been coined to designate those studies in which the control sampling is density-based (e.g. the control series represents the person-time distribution of exposure in the source population). The case-cohort is also a variant in which the control sampling is performed on those

persons who make up the source population regardless of the duration of time they may have contributed to it (2).

A case-control approach could also be set up as a permanent scheme to identify and quantify risks (case-control surveillance). This strategy has been followed for rare diseases with a relevant aetiology fraction attributed to medicinal products, including blood dyscrasias or serious skin disorders.

VIII.App1.1.2.4. Other designs

Other designs have been proposed to assess the association between intermittent exposures and short-term events, including the self-controlled case-series [VIII.App 1. Reference 8], the case-crossover [VIII.App 1. Reference 9] and the case-time-control [VIII.App 1. Reference 10] studies. In these designs, only cases are used and the control information is obtained from past person-time experience of the cases themselves. One of the important strengths of these designs is that those confounding variables that do not change within individuals are automatically matched.

VIII.App1.1.3. Clinical trials

When significant risks are identified from pre-approval clinical trials, further clinical trials might be called for to evaluate the mechanism of action for the adverse reaction. If the study is a clinical trial, provisionss of Directive 2001/20/EC shall apply. In some instances, pharmacodynamic and pharmacokinetic studies might be conducted to determine whether a particular dosing instruction can put patients at an increased risk of adverse events. Genetic testing may also provide clues about which group of patients might be at an increased risk of adverse reactions. Furthermore, based on the pharmacological properties and the expected use of the medicinal product in general practice, conducting specific studies to investigate potential drug-drug interactions and food-drug interactions might be called for. These studies may include population pharmacokinetic studies and drug concentration monitoring in patients and normal volunteers.

Sometimes, potential risks or unforeseen benefits in special populations might be identified from pre-approval clinical trials, but cannot be fully quantified due to small sample sizes or the exclusion of subpopulations of patients from these clinical studies. These populations might include the elderly, children, or patients with renal or hepatic disorder. Children, the elderly, and patients with co-morbid conditions might metabolise medicinal products differently than patients typically enrolled in clinical trials. Further clinical trials might be used to determine and to quantify the magnitude of the risk (or benefit) in such populations.

VIII.App1.1.3.1. Large simple trials

A Large simple trial is a specific form of clinical trial where large numbers of patients are randomised to treatment but data collection and monitoring is kept to the minimum, consistent with the aims of the study [VIII.App 1. Reference 11]. This design may be used in pharmacovigilance to elucidate the risk-benefit profile of a medicinal product outside of the formal/traditional clinical trial setting and/or to fully quantify the risk of a critical but relatively rare adverse event. The use of the term ‘simple’ refers to data structure and not data collection. It is used in relation to situations in which a small number of outcomes are measured and the term may not adequately reflect the complexity of the studies undertaken. These studies qualify as clinical trials.

VIII.App1.1.4. Drug utilisation studies

Drug utilisation studies (DUS) describe how a medicinal product is, prescribed and used in routine clinical practice in large populations, including elderly patients, children, pregnant women or patients

with hepatic or renal dysfunction, who are often excluded by randomized clinical trials. Stratification by age, gender, concomitant medication and other characteristics allows a comprehensive characterization of treated patients, including the distribution of those factors that may influence clinical, social, and economic outcomes. From these studies, denominator data may be derived for use in determining rates of adverse reactions. DUS have been used to describe the effect of regulatory actions and media attention on the use of medicinal products, as well as to develop estimates of the economic burden of adverse reactions. DUS may be used to examine the relationship between recommended and actual clinical practice. These studies may help to monitor use in everyday medical practice and medication error and to determine whether a medicinal product has potential for abuse by examining whether patients are taking escalating dose regimens or whether there is evidence of inappropriate repeat prescribing.

VIII.App1.2. Data sources

Pharmacoepidemiological studies may be performed using a variety of data sources. Traditionally, field studies were required for retrieving the necessary data on exposure, outcomes, potential confounders and other variables, through interview of appropriate subjects (e.g. patients, relatives) or by consulting the paper-based medical records. However, the advent of automated healthcare databases has remarkably increased the efficiency of pharmacoepidemiologic research. There are two main types of automated databases, those that contain comprehensive medical information, including prescriptions, diagnosis, referral letters and discharge reports, and those mainly created for administrative purposes, which require a record-linkage between pharmacy claims and medical claims databases. These datasets may include millions of patients and allow for large studies. They may not have the detailed and accurate information needed for some research, such as validated diagnostic information or laboratory data, and paper-based medical records should be consulted to ascertain and validate test results and medical diagnoses. Depending on the outcome of interest, the validation may require either a case-by-case approach or just the review of a random sample of cases. Other key aspects may require validation where appropriate. There are many databases in place for potential use in pharmacoepidemiological studies or in their validation phase.

Marketing authorisation holders should select the best data source according to validity (e.g. completeness of relevant information, possibility of outcome validation) and efficiency criteria (e.g. time span to provide results). External validity should also be taken into account: As far as feasible the data source chosen to perform the study should include the population in which the safety concern has been raised. In case another population is involved, the marketing authorisation holder should evaluate the differences that may exist in the relevant variables (e.g. age, sex, pattern of use of the medicinal product) and the potential impact on the results. In the statistical analysis, the potential effect of modification of such variables should be explored.

With any data source used, the privacy and confidentiality regulations that apply to personal data should be followed.

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