1 3 August 2015
2 EMA/813938/2011 Rev 2* - Draft for public consultation

3 Guideline on good pharmacovigilance practices (GVP)

4 Module VIII – Post-authorisation safety studies (Rev 2)

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Draft Revision 2* finalised by the Agency in collaboration with Member States	23 June 2015
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6 *Note: Revision 2 contains the following:

7 • Changes to VIII.A., clarifying the link between the legislation on non-interventional PASS and
8 categories 1-4 of non-interventional PASS described in GVP Module V;

9 • Changes to VIII.B.3.1., adding text in line with GVP Module VI Rev 1 to provide a
10 recommendation on adverse events that will not be collected or reported;

11 • Changes to VIII.B.3. and XIII.B.4. with the sentence referring to the notification of substantial
12 amendments to PASS protocols, progress reports and final reports to the Agency for centrally-
13 authorised products moved to GVP XIII Addendum I Rev 2;

14 • Changes to VIII.B.8. with additions from previous VIII.C.3., removing duplication of text;

15 • Changes to VIII.C.2.d., specifying that the definition of the core elements of a PASS protocol
16 will normally be a first step in the process leading to joint studies, prior to the agreement (or
17 not) of a joint study by different marketing authorisation holders;

18 • Updating of the structure to bring the Module in line with other GVP Modules as structuring has
19 consolidated over time (previous B.1. and C.1 on scope moved to A and previous B.2. moved
20 to A.1.);

- Editorial amendments throughout the Module;
- Revision of nearly all Sections of VIII.Appendix 1 in order to:
  - provide updated and more detailed information on some study designs;
  - revise the terminology where needed.

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

Note for public consultation:

The public consultation is restricted to the yellow highlighted revised texts (i.e. replaced by new texts with deletions and additions) or deleted texts (i.e. not replaced). However, if revisions or deletions impact or contradict other existing text, comments on such non-highlighted texts will be processed and taken into account for the finalisation process.

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VIII.A. Introduction

A post-authorisation safety study (PASS) is defined in Directive 2001/83/EC (DIR) Art 1(15) 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.

This Module concerns PASS which are clinical trials or non-interventional studies, with a main focus on non-interventional PASS. It does not address non-clinical safety studies.

A non-interventional PASS may be initiated, managed or financed by a marketing authorisation holder voluntarily or pursuant to an obligation imposed by a competent authority [DIR Art 107m(1), Regulation (EC) No 726/2004 (REG) Art 28b]. These studies shall be conducted in accordance with the following provisions:

- DIR Art 107m for all non-interventional PASS initiated, managed or financed by a marketing authorisation holder, including those:
  - imposed as an obligation in accordance with REG Art 9 and Art 10a and with DIR Art 21a and Art 22a (category 1 of studies in GVP Module V);
  - imposed as a specific obligation in the framework of a marketing authorisation granted under exceptional circumstances (category 2 of studies in GVP Module V);
  - required in the risk management plan (RMP) to investigate a safety concern or to evaluate the effectiveness of risk minimisation activities (category 3 of studies in GVP Module V); and
  - those that may provide safety information of less significance (category 4 of studies of GVP Module V);
- DIR Art 107n-q and Commission Implementing Regulation (EU) No 520/2012 (IR) Art 36-38 for categories 1 and 2 of studies in GVP Module V.

A PASS is non-interventional if the following requirements are cumulatively fulfilled (see 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 its scientific objectives. Non-interventional studies include database research or review of records where all the events of interest have already happened (this may include case-control, cross-sectional, cohort or other study designs making secondary use of data). 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 these studies, interviews, questionnaires and collection of blood samples may be performed as part of normal clinical practice.

If a PASS is a clinical trial, the provisions of Directive 2001/20/EC and of Volume 10 of The Rules Governing Medicinal Products in the European Union[1] shall be followed.

The purposes of this Module are to:

- provide general guidance for the transparency, scientific standards and quality standards of non-interventional PASS conducted by marketing authorisation holders ~~voluntarily or pursuant to an obligation imposed by a competent authority~~ (VIII.B.);
- describe procedures whereby competent authorities may impose on a marketing authorisation holder an obligation to conduct a clinical trial or a non-interventional study (VIII.C.1.), as well as the impact of this obligation on the risk management system (VIII.C.2.);
- describe procedures that apply to non-interventional PASS imposed as an obligation for the protocol oversight and reporting of results (VIII.C.2.) and for changes to the marketing authorisation following results (VIII.C.4.).

The guidance in VIII.B. applies to non-interventional PASS which are initiated, managed or financed by a marketing authorisation holder and conducted in the European Union (EU). This guidance should also be used for studies conducted outside the EU which have been imposed or required by an EU competent authority (categories 1, 2 and 3 of studies defined in GVP Module V). In VIII.B., some legal requirements which are applicable to studies conducted pursuant to an obligation are recommended to all PASS in order to support the same level of transparency, scientific standards and quality standards for all PASS. This applies, for example, to the format and content of study protocols, abstracts and final study reports. A distinction is made in the text between situations where the provision of the guidance represents a legal requirement or a recommendation. The guidance applies to studies initiated, managed or financed by a marketing authorisation holder as well as those conducted by a third party on behalf of the marketing authorisation holder. The guidance applies to studies that involve primary collection of safety data directly from patients and healthcare professionals as well as those that make secondary use of data previously collected from persons and healthcare professionals for another purpose.

Provisions in 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 the EU. Section VIII.C.1. applies to both interventional and non-interventional PASS. Sections VIII.C.2. and VIII.C.3. apply to non-interventional PASS.

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.A.1. Terminology

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 subject is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts [IR Art 37]. Simple counts in a database to support the development of the study protocol, for example to inform the sample size and statistical precision of the study, are not part of this definition.

End of data collection: the date from which the analytical dataset is completely available [IR Art 37].

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

Analytical dataset: the minimum set of data required to perform the statistical analyses leading to the results for the primary objective(s) of the study.

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

VIII.B. Structures and processes

VIII.B.1. Principles

In accordance with DIR Art 1(15), a post-authorisation study should be classified as a PASS when the main aim for initiating the study includes any of the following objectives:

- to quantify 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 or a population exposed to another medicinal product, class of medicinal products or other intervention as appropriate, and investigate risk factors, including effect modifiers;
- to evaluate risks of a medicinal product used in patient populations for which safety information is limited or missing (e.g. pregnant women, specific age groups, patients with renal or hepatic impairment or other relevant comorbidity or co-medication);
- to evaluate the risks of a medicinal product after long-term use;
- to provide evidence about the absence of risks;
- to assess patterns of drug utilisation that add knowledge regarding the safety of the medicinal product (e.g. indication, dosage, co-medication, medication errors);
- to measure the effectiveness of a risk minimisation activity.

Whereas the PASS design should be appropriate to address the study objective(s), the classification of a post-authorisation study as a PASS is not constrained by the type of design chosen if it fulfils the criteria as set in DIR Art 1(15). For example, a systematic literature review or a meta-analysis may be considered as PASS depending on their aim.

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 by the Pharmacovigilance Risk Assessment Committee (PRAC) and national competent authorities for the evaluation of study protocols and study reports. Relevant scientific guidance includes, amongst others, the ENCePP Guide on Methodological Standards in Pharmacoepidemiology[2], the ENCePP Checklist for Study Protocols[2], the Guideline on Conduct of Pharmacovigilance for Medicines Used by the Paediatric Population for Studies Conducted in Children[3], and the Guidelines for Good Pharmacoepidemiology Practices of the International Society of Pharmacoepidemiology (ISPE GPP)[4].

For studies that are funded by a marketing authorisation holder, including studies developed, conducted or analysed fully or partially by investigators who are not employees of the marketing

[2] http://www.encepp.eu/standards_and_guidances/index.html
[3] EMEA/CHMP/PhVWP/235910/2005; available on http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003764.pdf
[4] http://www.pharmacoepi.org/resources/guidelines_08027.cfm

authorisation holder, the marketing authorisation holder should ensure that the investigators are qualified by education, training and experience to perform their tasks. The research contract between the marketing authorisation holder and investigators should ensure that the study meets its regulatory obligations while permitting their scientific expertise to be exercised throughout the research process. In the research contract, the marketing authorisation holder should consider the provisions of the ENCePP Code of Conduct[5], and address the following aspects:

- rationale, main objectives and brief description of the intended methods of the research to be carried out by the investigator(s);
- rights and obligations of the investigator(s) and marketing authorisation holder;
- 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 adverse reactions and other safety data by investigators, where 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.

Non-interventional post-authorisation safety studies shall not be performed where the act of conducting the study promotes the use of a medicinal product [DIR Art 107m(3)]. This requirement applies to all studies and to all activities performed in the study, including for studies conducted by the personnel of the marketing authorisation holder and by third parties on behalf of the marketing authorisation holder.

Payments to healthcare professionals for participating shall be restricted to compensation for time and expenses incurred [DIR Art 107m(4)].

VIII.B.2. Study registration

In order to support transparency on non-interventional PASS and to facilitate exchange of pharmacovigilance information between the Agency, Member States and marketing authorisation holders, the marketing authorisation holder should make study information available in the EU electronic register of post-authorisation studies (EU PAS Register) maintained by the Agency and accessible through the European medicines web-portal[6]. Registration in the EU PAS Register also applies to studies conducted outside the EU, including non-interventional studies requested by non-EU regulatory authorities. The study protocol should be entered in the register before the start of data collection. Updates of the study protocol in case of substantial amendments, progress reports and the final study report should be entered in the register (preferably within two weeks after their finalisation). Study information should normally be submitted in English. If the study protocol or the study report is written in another language, the marketing authorisation should facilitate access to study information by including an English translation of the title, the abstract of the study protocol and the abstract of the final study report.

[5] http://www.encepp.eu/code_of_conduct/index.html
[6] http://www.encepp.eu/encepp_studies/indexRegister.shtml

Where prior publication of the protocol could threaten the validity of the study (for example, in studies with primary data collection where prior knowledge of the study objective could lead to information bias) or the protection of intellectual rights, a study protocol with redactions made by the marketing authorisation holder may be entered into the register prior to the start of data collection. These redactions should be justified and kept to the minimum necessary for the objective aimed by the redaction process. Whenever a redacted study protocol is published prior to the start of data collection, the title page of the protocol should include the mention "Redacted protocol" and the complete study protocol should be made available to the Agency and national competent authorities upon request. The complete study protocol should be entered in the register (preferably within two weeks after the end of data collection).

VIII.B.3. Study protocol

All non-interventional 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. An overview of study designs and databases frequently used in post-authorisation safety studies is provided in VIII.App.1. EU and national requirements shall be followed for ensuring the well-being and rights of the participants [DIR Art 107m(2)]. 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 non-interventional PASS initiated by the marketing authorisation holder pursuant to an obligation, see VIII.C.2. for the submission of the study protocol.

For these studies, requirements for submission of the study protocol for centrally and nationally authorised products are specified in GVP Module VIII Addendum I.

In order to ensure compliance of the marketing authorisation holder with its pharmacovigilance obligations, the qualified person responsible for pharmacovigilance (QPPV) or his/her delegate (see GVP Module I) should be involved in the review and sign-off of study protocols conducted in the EU. Where applicable, the marketing authorisation holder's pharmacovigilance contact person at national level should be informed of any study sponsored or conducted by the marketing authorisation holder in that Member State and have access to the protocol.

VIII.B.3.1. Format and content of the study protocol

The study protocol should include the following information:

1. **Title**: informative title including a commonly used term indicating the study design and the medicinal product, substance or medicinal product class concerned, and a sub-title with a version identifier and the date of the last version. If the study protocol has been registered in the EU PAS Register, subsequent versions of the protocol should mention on the title page "EU PAS Register No:" with the registration number.
2. **Marketing authorisation holder**: name and address of the marketing authorisation holder.
3. **Responsible parties**: names, titles, qualifications, addresses, and affiliations of all main responsible parties, including the main author(s) of the protocol, the principal investigator, a coordinating investigator for each country in which the study is to be performed and other relevant study sites. A list of all collaborating institutions and investigators should be made available to the Agency and national competent authorities upon request.
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) as referred to in Article 107m(5) of Directive 2001/83/EC
- Interim report(s) of study results, where applicable, in line with phases of data analyses
- Final report of study results.

Any other important timelines in the conduct of the study should be presented.

7. **Rationale and background**: short description of the safety hazard(s), the safety profile or the risk management measures that led to the initiation or imposition of the study, and short critical review of available published and unpublished data to explain 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 or imposed, and research objectives, including any pre-specified hypotheses and main summary measures.

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, including the rationale for any inclusion and exclusion criteria and their impact on the number of subjects available for analysis. Where 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 should be addressed separately, including operational definitions; potential confounding variables and effect modifiers should be specified.

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. Where the study will use an existing data source, such as electronic health records, any information on the validity of the recording and coding of the data should be reported. If data collection methods or instruments are tested in a pilot study, plans for the pilot study should be presented. If a pilot study has already been performed, a summary of the results should be reported. Involvement of any expert committees to validate diagnoses should be stated. 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 statistical precision.

9.6. **Data management**: data management and statistical programmes to be used in the study, including procedures for data collection, retrieval and preparation.

9.7. **Data analysis**: 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; statistical procedures to be applied to the data to obtain point estimates and confidence intervals of measures of occurrence or association, and sensitivity analyses.

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, extent of source data verification and validation of endpoints, storage of records and archiving of statistical programmes. 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 European Union requirements for ensuring the well-being and rights of participants in non-interventional post-authorisation safety studies.

11. **Management and reporting of adverse events/adverse reactions**: procedures for the collection, management and reporting of individual cases of suspected 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 studies where information on certain adverse events will not be collected (see GVP Module VI), the marketing authorisation holder should provide a justification for the overall approach to the collection of safety data in the protocol. Any reference to adverse events should be made using the appropriate level of the MedDRA classification (see GVP Annex IV). In case where information on certain adverse events will not be collected, this section should describe the channels and documents to be used to inform the healthcare professionals and consumers of the possibility to

report adverse reactions to the marketing authorisation holder or to the national spontaneous reporting system (see GVP Module VI).

In certain circumstances where suspected adverse reactions with fatal outcome will not be subject to expedited reporting as individual case safety reports (see GVP Module VI), each of these adverse reactions should be listed in a table using the appropriate level of the MedDRA classification with a rationale for not reporting them.

A statement should indicate if the study is a non-interventional post-authorisation study based on secondary use of data, for which the reporting of suspected adverse reactions in the form of individual case safety reports is not required (see GVP Module VI).

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

13. **References.**

The format of the study protocol should follow the Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies published by the Agency[7].

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 summary of their methods and results. The full report should be made available to the Agency and national competent authorities upon request. Feasibility studies that are part of the research process should be 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.

An annex should list all separate documents and list or include any additional or complementary information on specific aspects not previously addressed (e.g. questionnaires, case report forms), with clear document references.

VIII.B.3.2. Substantial amendments to the study protocol

The study protocol should be amended and updated as needed throughout the course of the study. Any substantial amendments 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 national competent authorities and the Agency should be informed immediately. 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 non-interventional PASS initiated by the marketing authorisation holder pursuant to an obligation, see VIII.C.2. for the submission of substantial amendments to the study protocol.

Requirements for transmission of substantial amendments to the study protocol are specified in GVP Module VIII Addendum I. ~~For PASS concerning centrally-authorised products, substantial amendments to the study protocol should also be transmitted to the Agency.~~

[7] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/10/WC500133174.pdf

VIII.B.4. Reporting of pharmacovigilance data to competent authorities

VIII.B.4.1. 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 may affect the risk-benefit balance of the medicinal product should be communicated immediately in writing as an Emerging Safety Issue to competent authorities of the Member States in which the product is authorised and to the Agency via email (P-PV-emerging-safety-issue@ema.europa.eu). Information affecting the risk-benefit balance of the medicinal product may include that arising from an analysis of adverse reactions and aggregated data.

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

VIII.B.4.2. Reporting of adverse reactions/adverse events

Adverse reactions/adverse events should be reported to competent authorities in accordance with the provisions of GVP Module VI. Procedures for the collection, management (including a review by the marketing authorisation holder if appropriate) and reporting of suspected adverse reactions/adverse events should be put in place and summarised in the study protocol. If appropriate, reference can be made to the pharmacovigilance system master file (see GVP Module II) but details specific to the study should be described in this section. For study designs where expedited reporting is not required, this should be stated in the study protocol.

VIII.B.4.3. Study reports

VIII.B.6.4.1 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 centrally-authorised products. 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 risk-benefit 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)]. Requirements for transmission of progress reports are specified in GVP Module VIII Addendum I. ~~For PASS concerning centrally-authorised products, progress reports should also be transmitted to the Agency.~~

The timing of the submission of progress reports should be agreed with the relevant competent authorities and specified in the study protocol when they have been agreed before the study commences. Safety findings should also be reported in the periodic safety update reports (PSURs) (see GVP Module VII) and the risk management plan (RMP) updates (see GVP Module V), where applicable. This does not preclude the submission of the final study report separately for formal assessment.

The content of the progress report should follow a logical sequence and should include all the available data that are 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. The progress report may also include any interim report of study results. After review of the report, additional information may be requested.

VIII.B.6.4.2. Final study report

The final study report should be submitted as soon as possible within 12 months of the end of data collection.

For non-interventional PASS initiated by the marketing authorisation holder pursuant to an obligation, see VIII.C.2. as regards submission of the final study report.

Requirements for transmission of the final study report are specified in Module VIII Addendum I. ~~For PASS concerning centrally authorised products, the final study report should also be transmitted to the Agency.~~

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 include the following information:

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. If the study has been registered in the EU PAS Register, the final study report should mention on the title page "EU PAS Register No:" with the registration number and the link to the study record.
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 main responsible parties, including the main author(s) of the protocol, the principal investigator, a coordinating investigator for each country in which the study is to be performed and other relevant study sites. A list of all collaborating institutions and investigators should be made available to the Agency and national competent authorities upon request.
5. **Milestones**: planned and actual dates for the following milestones:
   - Start of data collection
   - End of data collection or date of early termination, if applicable, with reasons for termination
   - Study progress report(s)
   - Interim report(s) of study results, where 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 EU PAS Register.
6. **Rationale and background**: short description of the safety concern(s) that led to the study being initiated or imposed, and short critical review of relevant published and unpublished data evaluating pertinent information and gaps in knowledge that the study is intended to fill.
7. **Research question and objectives**: research question and 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 and diagnostic criteria, 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 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
- 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 should include the following sub-sections:

10.1. **Participants**: numbers of study subjects 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 and adverse reactions**: summary of all adverse events/adverse reactions reported in the study, in line with requirements described in GVP Module VI. For certain study designs with secondary use of data such as case-control or retrospective cohort studies, particularly those involving electronic healthcare 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 conflicting with the findings of the completed post-authorisation safety study, and, where relevant, 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 format of the final study report should follow the Guidance for the format and content of the final study report of non-interventional post-authorisation safety studies published by the Agency[8].

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

[8] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000199.jsp&mid=WC0b01ac05800250b3

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, including dropouts;
8. Variables and data sources;
9. Results;
10. Discussion (including, where relevant, an evaluation of the impact of study results on the risk-benefit balance of the product);
11. Marketing authorisation holder;
12. Names and affiliations of principal investigators.

VIII.B.5. Publication of study results

For studies that are fully or partially conducted by investigators who are not employees of the marketing authorisation holder, the marketing authorisation holder and the investigator should agree in advance on a publication policy allowing the principal investigator to independently prepare publications based on the study results irrespective of data ownership. 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.

VIII.B.5.1. ~~Regulatory~~ Submission of manuscripts accepted for publication

In order to allow ~~national~~ competent authorities to review in advance the results and interpretations to be published, the marketing authorisation holder initiating, managing or financing a non-interventional PASS should communicate to the Agency and the competent authorities of the Member States in which the product is authorised the final manuscript of the article within two weeks after first acceptance for publication.

VIII.B.6. 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.

For PASS imposed as an obligation, the marketing authorisation holder shall ensure that all study information is handled and stored so as to allow for accurate reporting, interpretation and verification of that information and shall ensure that the confidentiality of the records of the study subjects remains protected [IR Art 36]. This provision should be applied for all PASS.

VIII.B.7. Quality systems, audits and inspections

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. For PASS imposed as an obligation, the marketing authorisation holder shall ensure that the analytical dataset and statistical programmes used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection [IR Art 36]. This provision should be applied for all PASS.

VIII.B.8. Impact on the risk management system

Non-interventional PASS imposed as an obligation (category 1 and 2 studies in GVP Module V) or required to investigate a safety concern of the RMP (category 3 of studies in GVP Module V) should be described in the RMP. 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. Finalised protocols for studies in the pharmacovigilance plan should be provided in RMP annex 6 until submission of the final study report to the competent authorities. Studies looking at the effectiveness of risk minimisation measures should be included in the pharmacovigilance plan as well as described in detail in the risk minimisation plan.

Other non-interventional PASS which are not obligations or required studies in the RMP but which could provide relevant information on the safety profile of the product (category 4 of studies in GVP Module V) should be listed in the RMP section III "Summary table of additional pharmacovigilance activities".

~~For studies imposed as an obligation, see also VIII.C.3.~~

VIII.C. Operation of the EU network

VIII.C.1. Procedure for imposing post-authorisation safety studies

In the EU, the conduct of any post-authorisation safety study (PASS) can be imposed during the evaluation of the initial marketing authorisation application [REG Art 9, DIR Art 21a] or during the post-authorisation phase [REG Art 10a, DIR Art 22a]. by the Agency or the national competent authority whenever there are concerns about the risks of an authorised medicinal product. This obligation shall be duly justified, and shall be notified in writing and shall include the objectives and timeframe for the submission and conduct of the study. The request should be based on benefit-risk considerations. The request may also include recommendations on key elements of the study (e.g. study design, setting, exposure(s), outcome(s), study population). ~~An overview of study designs and databases frequently used in post-authorisation safety studies is provided in VIII.App.1.~~

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

A marketing authorisation may be granted by the competent authority subject to the conduct of a PASS [REG Art 9, DIR Art 21a]. If, during the evaluation of a marketing authorisation application, the need for a PASS is identified by the PRAC for a centrally authorised product or a product authorised nationally through the mutual recognition or the decentralised procedure, the PRAC may adopt an advice with an assessment report to the Committee for Medicinal Products for Human Use (CHMP) or the Member States as applicable.

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

The need for a PASS could be identified by the Agency or a national competent authority during a post-authorisation regulatory procedure, for example, an extension or a variation to a marketing authorisation, a renewal procedure or a PSUR procedure. If, during the evaluation of a post-authorisation procedure, the need for a PASS is identified by the PRAC for a centrally authorised product or a product authorised nationally through the mutual recognition or the decentralised procedure, the PRAC may adopt an advice or a recommendation with an assessment report to the CHMP or the Member States 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 [REG Art 10a, DIR Art 22a] If the need for a PASS is identified by the PRAC for a centrally authorised product or a product authorised nationally through the mutual recognition or the decentralised procedure, the PRAC may adopt an advice with an assessment report to the CHMP or the Member States as applicable.

d. Joint post-authorisation safety studies

If safety concerns apply to more than one medicinal product, the Agency or the national competent authority shall, following consultation with the PRAC, encourage the marketing authorisation holders concerned to conduct a joint PASS [REG Art 10a, DIR Art 22a]. A joint PASS may also be necessary where there are limited patients (rare diseases) or the adverse reaction is rare. Requests to the marketing authorisation holders should contain the justification for the request of a joint study and may include core elements for the study protocol. Upon request from the marketing authorisation holders, the national competent authority or the Agency may provide suggestions for a joint study 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 define, in consultation with the PRAC, either a common core protocol or key elements (for example, the study design, the study population and the definition of exposure and outcomes) which each marketing authorisation holder will have to implement in the study protocol to be submitted to the national competent authority or the PRAC in accordance with DIR Art 107n(1).~~

e. Written observations in response to the imposition of an obligation

Within 30 days of receipt of the written notification of an obligation imposed after the granting of a marketing authorisation, the marketing authorisation holder may request the opportunity to present written observations in response to the imposition of the obligation [REG Art 10a(2), DIR Art 22a(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 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 [REG Art 10a(3), DIR Art 22a(3)] (see GVP Module V).

~~*VIII.C.3. Impact 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 VIII.B.10.) and their safety findings results will be provided presented within the PSUR following completion of the final report, where applicable (see GVP Module VII). This does not preclude the submission of the final study report separately for formal assessment.~~

~~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 annex 6 of the RMP.~~

~~When a RMP does not exist, a new RMP should be developed referring to the post-authorisation safety study.~~

VIII.C.2. Supervision of non-interventional post-authorisation safety studies conducted pursuant to an obligation

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 DIR Art 22a and conducted only in that Member State, in which case national oversight procedures apply [DIR Art 107n(1)].

VIII.C.2.1. Roles and responsibilities of the marketing authorisation holder

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 DIR Art 107m-q, in IR Art 36-38 and in VIII.B.. The marketing authorisation holder shall ensure the fulfilment of its pharmacovigilance obligations in relation to the study and that this fulfilment can be audited, inspected and verified (see VIII.B.6. and VIII.B.7.).

Following the imposing as a condition to the marketing authorisation 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)] as appropriate. When the PRAC is involved in the oversight of the study, the marketing authorisation holder shall submit the study protocol to the PRAC and to the Agency.

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 DIR Art 107m-q, in IR Art 36-38, in Module VIII.B and in 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 (see VIII.B.8. and VIII.B.9.).~~

The marketing authorisation holder shall develop the study protocol following the format of IR Art 38 and should consider the recommendations set out in VIII.B.3.1.. The study may commence only when the written endorsement from the national competent authority or the PRAC, as appropriate, has been issued. When a letter of endorsement has been issued by the PRAC, the marketing authorisation holder shall forward the protocol to the competent authority of the Member State(s) in which the study is to be conducted and may thereafter commence the study according to the 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)].

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.

After a non-interventional imposed PASS has been commenced, the marketing authorisation holder shall submit any substantial amendments to the protocol, before their implementation, to the national competent authority or to the PRAC, as appropriate (see VIII.A.1. for the definition of a substantial amendment). When the PRAC is involved in the oversight of the study, the marketing authorisation holder shall submit the amended study protocol to the PRAC and to the Agency.

The marketing authorisation holder may be requested to submit the study progress reports to the competent authorities in which the study is conducted [DIR Art 107m(5)].

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 IR Art 38, with consideration to the recommendations set out in VIII.B.4.3.2.. The public abstract shall follow the format of IR Art 38.

When the PRAC is involved in the oversight of the study, the marketing authorisation holder shall submit the final study report to the PRAC and to the Agency. When the PRAC is responsible for ~~regulatory~~ supervision of the PASS, 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 include a justification for the waiver. 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 marketing authorisation holder shall submit the study protocol, the abstract of the final study report and the final study report in English except for studies to be conducted in only one Member State that requests the study according to DIR Art 22a. For the latter studies, the marketing authorisation holder shall provide an English translation of the title and abstract of the study protocol as well as an English translation of the abstract of the final study report [IR Art 36].

VIII.C.2.2. Roles and responsibilities of the PRAC and national competent authority

When the PRAC is involved in the oversight of the study, the PRAC will nominate a PRAC rapporteur responsible for the supervision of the PASS. The PRAC rapporteur should draft a protocol assessment report 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 as appropriate 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;
- it is considered that the design of the study does not fulfil the study objectives [DIR Art 107n(2)].

In case of submission of an amended study protocol, 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]. The national competent authority or the PRAC will provide

the marketing authorisation holder with a letter of endorsement or objection to the protocol amendment within 60 days of submission. The letter of objection will provide a timeline by which the marketing authorisation holder should resubmit an amended version of the protocol.

Where the study protocol for a nationally authorised product through the mutual recognition or the decentralised procedure is assessed by a national competent authority, this national competent authority is invited to share its assessment with the other concerned Member States.

Concerning the assessment of study results, in cases where the PRAC is involved in the oversight of the study, the PRAC will produce an assessment report and issue a recommendation (when an action on the marketing authorisation is recommended) addressed to the CHMP or CMDh, as applicable.

VIII.C.2.3. Roles and responsibilities of the Agency

The Agency shall provide scientific secretariat to the PRAC.

~~Upon receipt of the study protocol and of the final study report submitted by the marketing authorisation holder the Agency will provide the PRAC rapporteur with a summary of the study protocol and of the final study report.~~

The Agency will inform the marketing authorisation holder in writing and within the appropriate timelines of the decisions of the PRAC with respect to the assessment of the following:

- Study protocol;
- Study protocol amendments;
- Final study report;
- Waiver request for the submission of the final study report.

When the marketing authorisation holder submits a request to the Agency for a pre-submission meeting, the Agency will be responsible for a timely set up of the meeting with the Agency and the PRAC rapporteur.

The Agency shall make public on the European medicines web-portal protocols and public abstracts of results of the post-authorisation safety studies referred to in DIR Art 107n and 107p.

VIII.C.3. Changes to the marketing authorisation following results from a non-interventional post-authorisation safety study

The marketing authorisation holder shall evaluate whether the study 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 as applicable 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 or a competent authority in a Member State may recommend variation, suspension or revocation of the marketing authorisation [REG Art 28b(2), DIR Art 107q(2)]. The recommendation by the PRAC shall mention any divergent positions and the grounds on which they are based [DIR Art 107q(1)].

The PRAC may make a recommendation for the variation, suspension or revocation of the marketing authorisation for centrally authorised products (or for several products including at least one centrally-

authorised product) and for nationally authorised products including those authorised by the Member States pursuant to Directive 2001/83/EU [Dir Art 107q(2)].

For centrally authorised products, or where at least one centrally-authorised product is concerned, the recommendation made by the PRAC shall be transmitted to the CHMP which shall adopt an opinion taking into account the recommendation. 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, 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 agreed position shall be sent by the CMDh to the marketing authorisation holder and Member States which 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 [DIR Art 107q(2)].

Where the agreement or position of the CMDh 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)].

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 DIR Art 33 and 34 [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.4.3.1.). In such case, an appropriate procedure will be initiated (see GVP Module VI).

VIII. Appendix 1. Methods for post-authorisation safety studies

VIII.App1.1. Study designs

Post-authorisation safety studies may adopt different designs depending on their objectives. A brief description of the main 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 information sources, such as the ENCePP Guide for Methodological Standards.

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 to be contacted at a later stage. 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. However, some of the limitations of spontaneous reporting systems still apply, especially when evaluating delayed effects. 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. 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 (potentially) causally related to the medication. Monitoring may also be focused on certain major events that tend to be medicine-related such as jaundice, renal failure, haematological disorders, or 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.

Intensive monitoring 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. Intensive monitoring 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. Prescription event monitoring

In prescription event monitoring (PEM), 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. PEM tends to be used as a method to study safety just after product launch and is akin to enhanced surveillance Limitations of prescription event monitoring include substantial loss to follow-up, relatively short duration of follow-up, selective sampling, selective reporting 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 (see VIII.App 1. References 6-7).

VIII.App1.1.1.3. Registries

A registry is an organised system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition or exposure. A registry can be used as a data source within which studies can be performed.

Entry in a registry is generally defined either by diagnosis of a disease, prescription of a medicinal product, or both (patients with a certain disease treated with a defined medicinal product, defined active substance or any medicine of a defined class of medicinal products). The choice of the registry population and the design of the registry should be driven by its objective(s) in terms of outcomes to be measured and analyses and comparisons to be performed.

Registries are particularly useful when dealing with a rare disease, rare exposure or special population. In many cases, registries can be enriched with data on outcomes, confounding variables and effect modifiers obtained from a linkage to an existing database.

Depending on their objective, registries may provide data on patient, disease and treatment outcomes, and of their determinants. Data on outcomes may include data on patient-reported outcomes, clinical conditions, medicines utilisation patterns and safety and effectiveness. Registries should normally not be used to demonstrate efficacy of a medicinal product. Rather, once efficacy has been demonstrated in randomised clinical trials (RCTs), patient registries may be useful to study effectiveness in heterogeneous populations, effect modifiers, such as doses that have been prescribed by physicians and that may differ from those used in RCTs, patient sub-groups defined by variables such as age, co-morbidities, use of concomitant medication or genetic factors, or factors related to a defined country or healthcare system.

Where adequate data are already available or can be collected, patient registries may be used to compare risks of outcomes between different groups. For example, a case-control study may be performed to compare the exposure to the medicinal product of cases of severe adverse reactions identified from the registry and of controls selected from either patients within the registry or from outside the registry. Case-only designs may also be applied (see VIII.App 1.1.2.4.).

Patient registries may address exposure 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 medicinal product authorised 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, active surveillance programmes or case series. Major types of these designs are cross-sectional studies, case-control studies, and cohort studies, based on primary data collection or secondary use of existing data.

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 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 study participant. A study participant might be exposed to a medicinal product at one time during follow-up, but unexposed 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. They are also useful for the evaluation of multiple adverse events within the same study. However, it may be difficult to recruit sufficient numbers of patients who are exposed to a product of interest (such as an orphan medicinal product) 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 (older persons, 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.

VIII.App1.1.2.3. Case-control study

In a case-control study, cases of disease (or events) are identified and patients from the source population that gave rise to the cases but who do not have the disease or event of interest at the time of selection are then selected as controls. The odds of exposure is then compared between the two groups. Patients may be identified from an existing database or using a field study approach, in which data are collected specifically for the purpose of the case control study. If safety information is sought for special populations, the cases and controls may be stratified according to the population of interest (e.g. the older persons, children, pregnant women). 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 multiple risk factors for adverse events. Risk factors may include conditions such as renal and hepatic dysfunction, which might modify the relationship between the

exposure to the medicinal product and the adverse 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, a case-control study may also provide the absolute incidence rate of the event.

When the source population for the case-control study 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.~~

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, the case-crossover and the case-time-control studies. In these designs, only cases are used and the control information is obtained from person-time experience of the cases themselves. One of the important strengths of these designs is that those confounding variables that do not change over time within individuals are automatically matched. However, case-only designs cannot be used under all circumstances, for instance when the exact date of disease onset is difficult to establish or when evaluating chronic exposures.

VIII.App1.1.3. Clinical trials

When important 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, provisions of Directive 2001/20/EC shall apply. In some instances, pharmacodynamic and pharmacokinetic studies might be conducted to determine whether a particular dosing regimen 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 clinical 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 therapeutic drug 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 older persons, women of childbearing potential, children, or patients with renal or hepatic disorders. Children, older persons, and persons 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 to be a relatively low burden. 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 limited information is collected regarding exposure, outcome and potential confounders to help ensure feasibility of recruiting large patient numbers in an experimental design, and the term may not adequately reflect the complexity of the studies undertaken. These studies qualify as clinical trials. Pragmatic trials are a kind of large simple 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 older persons, children, pregnant women or patients with hepatic or renal dysfunction, who are often not eligible for inclusion in randomised clinical trials. Stratification by age, sex, 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, in some cases denominator data may be derived for use in determining rates of adverse events. 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. DUS are particularly useful as a first step in the design of post-authorisation safety studies, to obtain sufficient understanding of the characteristics of the user population of the medicinal product under study and the determination of the most appropriate comparator as well as important potential confounders to consider.

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 pharmacoepidemiological research. Generally, 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. A major limitation however often is the lack of long-term follow up and the consequent left- and right-censoring of data. In addition, these databases 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 analyses, 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 adhered to.