EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 July 2013
EMA/48663/2013
Patient Health Protection

Guidance for the format and content of the final study report of non-interventional post-authorisation safety studies

Introduction

From 10 January 2013, marketing authorisation holders have the obligation to comply with the format of the final study report for non-interventional post-authorisation safety studies (PASS), as specified in Art 36 to 38 and Art 40 of the Commission Implementing Regulation (EU) No 520/2012.

This document provides guidance for writing the final study report for non-interventional PASS in order to support the consistency of the information provided and facilitate its assessment. The guidance is based on Annex III(3) of Commission Implementing Regulation No 520/2012 with the additional instructions of Module VIII of the Good pharmacovigilance practices (GVP).[1]

This document also provides guidance for the Format of the abstract of the final study report referred to in Annex III(2) of Commission Implementing Regulation No 520/2012 (see Section 1. Abstract). This abstract serves as the abstract of the study results to be published by the Agency. For this purpose, the abstract should be uploaded in the "Study results" section of the EU PAS register. The marketing authorisation holder should also upload the full final study report in the register as an "Other document".[2]

The final study report should provide enough information on the design, conduct and analysis of the study so that there is no ambiguity in how the research question was addressed and how the study was carried out. In describing the research methods (section 9), it may be sufficient to restate in each section the corresponding description of the protocol if it is still valid. It is also possible to include the final version of the protocol in an Annex and summarise the main features of the study design in the final study report with references to the corresponding section of the protocol. Where the study was conducted or analysed differently from the specifications included in the protocol, this should be clearly mentioned and the deviations should be described.

All headings and sub-headings of the format presented in this guidance should always be included and the same numbering should be used. Additional sub-headings can be added as necessary. Where a

[1] The format of the study report is also derived from the *STROBE Statement* (http://www.strobe-statement.org/).
[2] the ENCePP E- Register of studies serves as the EU PAS register before it is operational (http://www.encepp.eu/encepp_studies/indexRegister.shtml

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heading or sub-heading does not apply to the study, it should still be included but "Not applicable" should be stated with a short justification. The same format for dates should be used throughout the report. The format "DD Month YYYY" (e.g. 01 January 2013) is recommended. The format DD-MMM-YYYY (e.g. 01-JAN-2013) may be used.

Annex 1 should be used to list clearly identifiable stand-alone documents not included in the final study report and available upon request, e.g. contact details of all responsible parties and of all investigators, or section 9.10. In this case, a summary should be provided in the corresponding section of the final study result and reference should be made to Annex 1. Other annexes can be added.

The final study report should be signed by the principal investigator. The qualified person in pharmacovigilance (QPPV) or his/her delegate should receive a copy of the report.

The text in italics and inserted between square brackets is intended to guide the reader on the principal points to be considered for writing that section of the final study report. It should be deleted if this guidance is used as a template.

For questions on this guidance, contact p-pv-helpdesk@ema.europa.eu with the Subject "Questions on guidance for PASS submission".

This guidance may be later revised based on comments and experience.

Revision 1 (dated 30 July 2013) includes changes in section 11 (Discussion) and 13 (Conclusion) in order to highlight the need to discuss the impact of the study results on the benefit-risk balance of the concerned product(s) and to remove redundancies.

PASS information

[PASS information should be provided in a table on the title page of the final study report.]

Title	*[Informative title including a commonly used term indicating the study design and the medicinal product, substance or drug class concerned]*
Version identifier of the final study report	*[Number (note: this version identifier is needed in case of resubmission of the final study report based on comments from the competent authority)]*
Date of last version of the final study report	*[Date]*
EU PAS register number	*[Registration number in the EU PAS register]*
Active substance	*[List of pharmacotherapeutic group(s) [ATC code(s)] and active substance(s) subject to the study]*
Medicinal product	*[List of centrally authorised medicinal product(s) and/or, if possible, of nationally authorised products subject to the study]*
Product reference	*[Reference number(s) of centrally authorised products and/or, if possible, of nationally authorised products subject to the study]*
Procedure number	*[If applicable, Agency or national procedure number(s), e.g. EMA/X/X/XXX]*
Marketing authorisation holder(s)	*[Marketing authorisation holder(s) which initiated, managed or financed the study]*
Joint PASS	*["Yes" or "No"]*
Research question and objectives	*[Summary of the research question and main objectives- max. 150 words]*
Country(-ies) of study	*[List of countries where the study has been conducted]*
Author	*[Name and contact details of the main author of the final report of the study]*

Marketing authorisation holder(s)

Marketing authorisation holder(s)	*[Name, address and contact details of the marketing authorisation holder(s)]*
MAH contact person	*[Contact person for this PASS final study report submission (if this a joint PASS, only one person should be mentioned)]*

Table of contents

[The final study report should include a table of contents including headings and sub-headings. The following table of contents can be used if this guidance serves as a template (select the table of content and press "F9" to update the page numbers).]

1. Abstract

[Stand-alone summary of the final study report including all the sub-sections below. For the content of the abstract, refer to the guidance provided for each section of the final study report and select the most relevant information. The abstract should normally contain less than 500 words excluding headings and the following sections: title, keywords, marketing authorisation holder(s), names and affiliations of principal investigators].

Title

[The title should include subtitles including the date of the abstract and the name and affiliation of the main author.]

Keywords

[Not more than five keywords indicating the main study characteristics.]

Rationale and background

Research question and objectives

Study design

Setting

Subjects and study size, including dropouts

Variables and data sources

Results

Discussion

[The discussion should include a conclusion and, where relevant, an evaluation of the impact of study results on the benefit-risk balance of the product.]

Marketing Authorisation Holder(s)

Names and affiliations of principal investigators

2. List of abbreviations

[List of main abbreviations used in the final study report]

3. Investigators

[List of name and affiliation of the principal investigator, a coordinating investigator for each country in which the study is to be performed and investigators in other relevant study sites. Contact details and the list of all investigators can be kept in a stand-alone document to be listed in Annex 1 and to be provided upon request.]

4. Other responsible parties

[Other responsible parties should be listed here.

In case of a Joint PASS, any sharing of responsibilities (eg. for management of adverse events) or distribution of tasks between marketing authorisation holders and other responsible parties should be mentioned in this section. Contact persons for each marketing authorisation holder should be mentioned. Other parties involved in the governance of the study should also be mentioned here, such as a scientific committee, an advisory board or a data review committee, with a short description of their roles and responsibilities and the list and affiliation of their members. This section should also list any contractor involved in the conduct of the study and not listed as investigator.]

5. Milestones

[Planned and actual dates for study milestones should be indicated in a table as indicated below. Milestones between <> are optional and should be included only if applicable. Planned dates should be those indicated in the final version of the study protocol. The column "Comments" should be used to provide a short explanation on differences between planned and actual dates.

Start of data collection and End of data collection are defined in Module VIII of the GVP (where the study uses data from existing electronic databases such as claims, prescriptions or health care records, "secondary use of data" applies to these definitions).

In case where the study protocol and any amendments needed to be reviewed by an Independent Ethics Committee (IEC) or Institutional Review Board (IRB), the date of approval should be included in the table. If approval was needed from many IECs or IRBs, the table may include the dates of first and last approvals and the list of all IECs or IRBs consulted should be provided in an Annex with the dates of approval. Other important milestones can be added.]

Milestone	Planned date	Actual date	Comments
Start of data collection	*[Date]*	*[Date]*	*[Text]*
End of data collection	*[Date]*	*[Date]*	*[Text]*
Registration in the EU PAS register	*[Date]*	*[Date]*	*[Text]*

Milestone	Planned date	Actual date	Comments
<Study progress report 1>	*[Date]*	*[Date]*	*[Text]*
<Study progress report 1>	*[Date]*	*[Date]*	*[Text]*
<Study progress report 1>	*[Date]*	*[Date]*	*[Text]*
<Interim report 1>	*[Date]*	*[Date]*	*[Text]*
<Interim report 1>	*[Date]*	*[Date]*	*[Text]*
<Interim report 1>	*[Date]*	*[Date]*	*[Text]*
Final report of study results	*[Date]*	*[Date]*	*[Text]*

6. Rationale and background

[Short description of the benefit-risk issue, safety concern or 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 should cite the findings of similar studies, and the expected contribution of the current study.]

7. Research question and objectives

[Research question that explains how the study has addressed the issue which led to the study being initiated or imposed, and research objectives, including any pre-specified hypotheses and main summary measures. Objectives may be organised as primary or secondary objectives where applicable.]

8. Amendments and updates

[Write "None" or indicate any substantial amendment and update to the study protocol after the start of data collection in a table as indicated below. If the final version of the protocol is included in Annex, a summary of the amendments can be provided in this section and reference can be made to the corresponding section of the protocol where all substantial amendments are described.]

Number	Date	Section of study protocol	Amendment or update	Reason
1	*[Date]*	*[Text]*	*[Text]*	*[Text]*
2	*[Date]*	*[Text]*	*[Text]*	*[Text]*
…	*[Date]*	*[Text]*	*[Text]*	*[Text]*

9. Research methods

[Description of the research methods, including:]

9.1. Study design

[Summary of the overall research design and rationale for this choice, including key elements of the design, such as the primary and secondary endpoints and the main measure(s) of effect. The strength of the study design to answer the research question may be explained in this section.]

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 for the study population. Methods of selection of study subjects should be described, including any inclusion and exclusion criteria and, where relevant, specific disease requirements for inclusion and methods for case ascertainment. Where the study design required sampling of study subjects, for example sampling of controls in a case-control study or analysis, the sampling method should be explained. If matching has been performed, matching criteria should be given. In case of secondary use of data, any eligibility of study subjects in terms of admission criteria in the database, duration of recording or quality of records should be described.]

9.4. Variables

[All outcomes, exposures, potential confounders and effect modifiers, including operational definitions and diagnostic criteria, if applicable. If the study addresses medicinal product(s), information relevant to the interpretation of the results should be provided on the product, e.g. route and mode of administration, dose or duration of exposure.]

9.5. Data sources and measurement

[For each variable of interest, source(s) of data and details of methods of collection 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. Any method for adjudication of outcomes (for example, independent review by more than one investigator with procedure to solve disagreements) should be described.

In case of a systematic review or meta-analysis, this section should include a 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

[Description of any efforts to assess and address potential sources of bias. If blinded determination of exposure or outcome was performed, the method to establish and maintain blindness should be described.]

9.7. Study size

[Study size, rationale for any sample size calculation, any method for attaining projected study size, and any power calculation.]

9.8. Data transformation

[Data management and 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

9.9.1. Main summary measures

[Measures used to summarise the data (e.g. mean, median, incidence rate, relative risk, etc.) and show their dispersion.]

9.9.2. Main statistical methods

[Statistical methods and models applied to the study, including those used to control for confounding and examine subgroups and interactions. The rationale for using a particular statistical method or model should be stated. In statistical analyses involving multivariate modelling, the method for variable introduction and criteria for variable selection should be described. For study designs involving computation of follow-up time for study subjects, this section should explain how the follow-up time has been distributed among relevant categories (e.g. exposure categories or risk periods) and accounted for in the statistical analysis, preferably by use of graphs, and how gaps in knowledge about exposure (e.g. during hospitalisations) were accounted for.

For meta-analyses, this section should describe methods for combining results of studies.]

9.9.3. Missing values

[How missing data were addressed.]

9.9.4. Sensitivity analyses

[Any sensitivity analyses performed on the data, how and why.]

9.9.5. Amendments to the statistical analysis plan

[Statistical analyses not foreseen in the statistical plan or deviating from the statistical plan, with rationale.]

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. Tables and figures may be included in the text or in a separate appendix at the end of the report (but before the Annexes described below) or both (e.g. summary tables in the text, full tables in an appendix).

This section should include the following sub-sections:]

10.1. Participants

[Clear accounting of study subjects who entered each stage of study, e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing followed and analysed. Reasons for non-participation at any stage should be mentioned. Flowcharts or diagrams should be used to display this information. The exact number of subjects included in analyses conducted for different objectives or hypotheses should be presented. 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

[Data for important characteristics of study subjects (e.g. age, sex, centre, categories of matching variables), potential confounders and other variables relevant to the study question, presented by exposure or outcome categories by use of tables, 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 subjects 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. Analyses made for different study objectives or hypotheses should be clearly separated. Unplanned analyses performed secondarily, such as sub-group analyses or investigation of alternative exposure categories, should be clearly identified and presented as exploratory.]

10.5. Other analyses

[Other analyses done, e.g. sensitivity analyses not included in 10.4, analyses of subgroups and interactions, analyses per centre or other relevant variables.]

10.6. Adverse events/adverse reactions

[For studies where solicited adverse events were listed in the protocol, these adverse events should be presented and discussed in this section. All other suspected adverse reactions notified by investigators and assessed at the individual case level should be presented and discussed in terms of seriousness and information available in the Summary of Product Characteristics. The presentation of adverse events/adverse reactions should be supported by summary tabulations of adverse events/adverse reactions. Detailed tabulations may be included in an appendix. When the Medical Dictionary for Regulatory Activities (MedDRA) terminology is used for coding the adverse reaction terms, the preferred term (PT) level and system organ class (SOC) should be presented in the summary tabulations. The table should be organised by MedDRA SOC (listed in the internationally agreed order). For special issues or concerns, additional tabulations of adverse events/adverse reactions can be presented by indication, route of administration or other variables.

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. Any risk identified from an aggregate analysis of the data and which is not an outcome of the study (or part of a sensitivity analysis) should be mentioned in this section.]

11. Discussion

11.1. Key results

[Key results with reference to the study objectives.]

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. Possible multiplicity of analyses and both direction and magnitude of potential biases should be discussed*.]

11.3. Interpretation

[Overall interpretation of results considering objectives, limitations and findings from similar studies and other relevant evidence supporting or conflicting with the study results. Results should also be interpreted in relation to the safety issue leading the study to be imposed or initiated, their impact on the benefit-risk balance of the concerned product(s) and the information included in the summary of product characteristics and the risk management plan of the product(s).]

11.4. Generalisability

[The generalisability (external validity) of the study results, considering the data source, characteristics of the study population, inclusion and exclusion criteria.]

12. Other information

[Any additional or complementary information on specific aspects not previously addressed.]

13. Conclusion

[Main conclusion of the study, deriving from the analysis of the data, including a statement regarding the impact of the study results on the benefit-risk balance of the product(s).]

14. References

[List of references using the Vancouver style].

Appendices

Annex 1. List of stand-alone documents

[Documents listed in Annex 1 can be maintained separately from the study final study report. They should be clearly identifiable and provided on request. Write "None" if there is no document or list documents in a table as indicated below.]

Number	Document reference number	Date	Title
1	*[Number]*	*[Date]*	*[Text]*
2	*[Number]*	*[Date]*	*[Text]*
…	*[Number]*	*[Date]*	*[Text]*

Annex 2. Additional information

[Additional annexes may be included if necessary.]