



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 September 2012
EMA/623947/2012
Patient Health Protection

Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies

Introduction

From 10 January 2013, marketing authorisation holders have the obligation to comply with the format and content of the study protocol for post-authorisation safety studies (PASS), as specified in Art 36 to 38 and Art 40 of the Commission Implementing Regulation (EU) No 520/2012. Use of the format is encouraged for PASS protocols submitted before that date.

This document provides guidance for drafting the study protocols for non-interventional PASS in order to support consistency of the presentation and information provided. The template is based on Art 38 of Implementing Regulation No 520/2012 with the additional instructions of Module VIII of the Good pharmacovigilance practices. For interventional PASS, instructions provided in Volume 10 of the Rules Governing Medicinal products in the European Union should be followed.

The study protocol should be concise, while providing the information needed to understand how the study will answer the research question and assess the validity of the study design.

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 heading or sub-heading does not apply to the study (eg. Protection of human subjects), "Not applicable" should be stated with a short justification. All dates should be indicated in the format "DD Month YYYY" (e.g. 24 June 2012). Annex 1 should be used to list stand-alone documents not included in the protocol, e.g. contact details of responsible parties and all investigators, or sections 9.6. Data management, 9.8. Quality control and 10. Protection of human subjects, which can be maintained apart from the study protocol where they



represent standard procedures applied to all studies. In this case, a summary should be provided in the corresponding section of the protocol and reference should be made to Annex 1. Annexes can be added to provide documents referred to in the protocol.

The text in green italics is intended to guide the reader on the principal points to be considered for writing that section of the protocol. It should be deleted if this guidance is used as a template.

It is reminded that the marketing authorisation holder(s) involved should keep a copy of the protocol signed by the qualified person in pharmacovigilance (QPPV) or his/her delegate (with the date of the signature) available for any future request or inspection.

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

This guidance may be later revised based on experience.

PASS information

PASS information should be provided in a table on the title page of the study protocol.

Title	<i>Informative title including a commonly used term indicating the study design and the medicinal product, substance or drug class concerned</i>
Protocol version identifier	<i>Number</i>
Date of last version of protocol	<i>Date</i>
EU PAS register number	<i>Registration number in the EU PAS register; indicate "Study not registered" if the study has not been registered in the EU PAS register.</i>
Active substance	<i>List of pharmacotherapeutic group(s) (ACT codes) and active substance(s) subject to the study</i>
Medicinal product	<i>List of centrally authorised medicinal product(s) and/or, if possible, of nationally authorised products subject to the study</i>
Product reference	<i>Reference number(s) of centrally authorised products and/or, if possible, of nationally authorised products subject to the study</i>
Procedure number	<i>If applicable, Agency or national procedure number(s), e.g. EMA/X/X/XXX</i>
Marketing authorisation holder(s)	<i>Marketing authorisation holder(s) which initiate(s), manage(s) or finance(s) the study</i>
Joint PASS	<i>"Yes" or "No"</i>
Research question and objectives	<i>Summary of the research question and main objectives</i>
Country(-ies) of study	<i>List of countries where the study is to be conducted; if countries have not been identified yet, or if the list is not complete, this should be stated</i>
Author	<i>Name and contact details of the main author of the study protocol</i>

Marketing authorisation holder(s)

Marketing authorisation holder(s)	<i>Name, address and contact details of the marketing authorisation holder(s).</i>
MAH contact person	<i>Contact person for this PASS protocol submission (if this a joint PASS, only one person should be mentioned)</i>

1. Table of contents

The study protocol should include a table of contents. 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).

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2. List of abbreviations

List of main abbreviations used in the study protocol

3. Responsible parties

List of all main responsible parties, including the principal investigator, a coordinating investigator for each country in which the study is to be performed and 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 available upon request.

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.

4. Abstract

Stand-alone summary of the study protocol including all of the sub-sections below.

Title

The title should include 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

"Population" includes the setting and study population.

Variables

Data sources

Study size

Data analysis

Milestones

5. 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.

Number	Date	Section of study protocol	Amendment or update	Reason
1	<i>Date</i>	<i>Text</i>	<i>Text</i>	<i>Text</i>
2	<i>Date</i>	<i>Text</i>	<i>Text</i>	<i>Text</i>
...	<i>Date</i>	<i>Text</i>	<i>Text</i>	<i>Text</i>

6. Milestones

Planned dates for study milestones should be indicated in a table as indicated below. Milestones between <> are optional and should be included only if applicable. 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). Other important timelines can be added.

Milestone	Planned date
Start of data collection	<i>Date</i>
End of data collection	<i>Date</i>
<Study progress report 1>	<i>Date</i>
<Study progress report 1>	<i>Date</i>
<Study progress report 1>	<i>Date</i>
<Interim report 1>	<i>Date</i>
<Interim report 1>	<i>Date</i>
<Interim report 1>	<i>Date</i>
<Registration in the EU PAS register>	<i>Date</i>
Final report of study results	<i>Date</i>

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. Objectives should be organised as primary or secondary objectives where applicable.

9. Research methods

Description of the research methods, including:

9.1. Study design

Overall research design and rationale for this choice, specifying the study design proposed (cohort, case-control, etc.) and any comparison groups. The primary and secondary endpoints and the main measure(s) of effect should be mentioned. The strength of the study design to answer the research question may be explained in this section.

9.2. Setting

Setting and study population defined in terms of persons, place, study time period, and selection criteria, including the rationale for any exclusion criteria and their impact on the number of subjects available for analysis. Plans for baseline visits and follow-up visits should be described. Representativeness of the study population as regards the source population should be addressed. 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

Definition of exposures, outcomes, and other variables including measured risk factors, co-morbidities, co-medications, etc. with operational definitions and measurement; 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 is based on secondary analysis an existing data source, such as electronic health records or claims databases, any information on the validity of the recording and coding of the data should be reported. For exposures or outcomes not previously validated, validation performed in the study should be described or otherwise addressed. Linkage methods between data sources should be described as appropriate. 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. All assumptions used to calculate the study size or precision of the study should be presented and justified.

9.6. Data management

Data management and statistical software(s) to be used in the study, including procedures for data collection, retrieval, collection and preparation.

Data collection methods and tools (e.g. paper-based or electronic case reporting forms, monitoring if any and supervision) can be summarised in this section and fully described or presented in an Annex.

9.7. Data analysis

Rationale for the choice of statistical techniques and 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 the statistical programming performed to generate the results. 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.

9.10. Other aspects

Any other aspect of the research method not covered by the previous sections.

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 adverse events/adverse reactions (see GVP Module VI) 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 reporting is not required, this should be stated. Any arrangements made between marketing authorisation holders for the management and reporting of adverse events/reactions in Joint PASS should be specified.

12. Plans for disseminating and communicating study results

Any plans for submission of progress reports and final reports; any arrangements made between marketing authorisation holders for the disseminating and communicating study results of Joint PASS.

13. References

Numbered list of literature or electronic references of documents referred to in the protocol. Sufficient information should be provided to allow retrieval of the document.

Annex 1. List of stand-alone documents

Documents listed in Annex 1 can be maintained separately from the study protocol. 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	<i>Number</i>	<i>Date</i>	<i>Text</i>
2	<i>Number</i>	<i>Date</i>	<i>Text</i>
...	<i>Number</i>	<i>Date</i>	<i>text</i>

Annex 2. ENCePP checklist for study protocols

A copy of the ENCePP Checklist for Study protocols available at http://www.encepp.eu/standards_and_guidances/index.html completed and signed by the main author of the study protocol should be included in Annex 2.

The checklist will facilitate the review of the protocol and evaluation of whether investigators have considered important methodological aspects.

In question 9.5 of the Checklist, Revision 1:

"Study start" means "Start of data collection"

"Study progress" means "Progress report(s)"

"Study completion" means "End of data collection"

"Reporting" means "Final report of the study results"

Annex 3. Additional information

Additional annexes may be included if necessary.