SCOPE Work Package 8
Lifecycle Pharmacovigilance

Practical Guide on PASS Assessment

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SCOPE

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Contents

Acknowledgments

This document is developed and adopted with participation of all WP8 contributors*.

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1. Introduction

1.1 Purpose of the document

The purpose of this document is to provide practical guidance from WP8 Lifecycle Pharmacovigilance, Post-Authorisation Safety Studies (PASS) assessment. The practical guide covers assessment of both PASS protocols and study reports. The draft scientific guidance on Post-Authorisation Efficacy Studies (PAES) has been released for public consultation on 06/11/2015, along with the post-authorisation guidance on PAES. However the practical experiences for assessment of PAES is currently limited.

The WP8 lead is Italy; the topic lead is Sweden, in collaboration with Italy, Ireland, Spain, Portugal, UK and Norway.

The following aspects should be considered:

- This document is intended to give practical guidance on some aspects of PASS assessment and drafting of Assessment Reports (ARs). It is not intended in any sense to replace PASS guidance and requirements detailed elsewhere. It is not intended to advise on procedural and scientific aspects or to influence templates and guiding text provided by the EMA.
- Assessors need to be familiar with legislation and guidelines and to refer to these as appropriate throughout the assessment process.

1.2 Relevant guidelines

- Guidance for the format and content of the protocol of non-interventional PASS
- Guidance for the format and content of the final study report of non-interventional PASS
- Scientific guidance on PAES (Draft)
- Template for PRAC/Rapporteur PASS protocol preliminary/updated assessment
- Template for PRAC/Rapporteur Preliminary/Updated Assessment report of an non-interventional imposed PASS final study report

1.3 Definitions and abbreviations

Terminology	Description
AEMPS	La Agencia Española de Medicamentos y Productos Sanitarios
AR	Assessment Report
CCAA	Comunidades autonomas/Autonomous Communities in Spain
EnCepp	The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EMA	European Medicines Agency
EU	European Union
GVP	Good pharmacovigilance practices
IFPMA	International Federation of Pharmaceutical Manufacturers & Associations
ISPE	International Society for Pharmaceutical Engineering
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
MAH	Marketing Authorisation Holder
MS	Member State
NCA	National Competent Authority
PAES	Post-Authorisation Efficacy Study
PASS	Post-Authorisation Safety Studies
PV	Pharmacovigilance
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PSUSA	Single assessment of Periodic Safety Update Reports
RECORD	REporting of studies Conducted using Observational Routinely-collected health Data
RMM	Risk Minimisation Measure
RMP	Risk Management Plan
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
WP	Work Package

2. Background

The continued benefit/risk assessment of a medicinal product during its lifecycle and consistency in the application and evaluation of risk management and minimisation principals are the cornerstones for the effective operation of the pharmacovigilance (PV) system in the European Union (EU). At the time of authorisation of a new medicinal product, the known important safety concerns (risks and missing information) are summarised in the Risk Management Plan (RMP).

The possibility to request PASS or PAES gives the National Competent Authority (NCA) more tools for planning how to further characterise already identified risks or further evaluate important potential risks, and how to gather information on gaps in knowledge in specific subpopulations. Such studies are described in the PV Plan of the RMP. A PASS is not a specific study design. It can be non-interventional or interventional. The study methods in this field, including active surveillance (such as intensive monitoring schemes, prescription event monitoring and registries), observational studies (such as cohort, case-control, cross-sectional studies or with other designs including self-controlled case-series, case-crossover and case-time-control studies), clinical trials (such as mechanistic, pharmacodynamic, pharmacokinetic or interaction studies, including large simple trials), and drug utilisation studies, continue to develop. In this "practical guide" document, only non-interventional studies are discussed.

2.1 Need for PASS?

The first question to raise is whether a safety concern could be followed by routine PV, i.e. signal detection, or not. If the safety question concerns changed frequency, or further characterisation of an important identified risk is needed, then there needs to be an additional PV study, such as PASS.

Common concerns in the RMP regarding important potential risks that lead to PASS include: Estimate the strength of a potential association between exposure to the medicine and specified adverse events: Are there changes in incidence over time for an adverse event? Can specific risk groups within the approved indication(s) be identified? How common is off-label use?

A clearly specified scientific question based on the safety concern is important in order to improve the chances to obtain an interpretable result from PASS that can support regulatory decision-making.

3. Challenges/limits

The advice on good practice provided in this document was extrapolated from the WP8 survey report and has been further elaborated on the basis of the comments and discussions raised by participants during the WP8 meetings and consultations.

One of the challenges in identifying current practice at national level is the fact that not all European NCAs have participated in the SCOPE project; thus, the document only reflects the practice in SCOPE participating countries.

Some NCAs did not answer all questions in the survey, in particular in areas such as PASS and PAES where some NCAs have little experience.

Differences between Member States (MSs), e.g. in having experience as PRAC rapporteur, as well as different resources and priorities, may make it difficult to generalise the results.

4. Practical guidance

4.1. Practical approach (planning, organisation and pre-assessment preparatory work)

4.1.1. Planning and organisation

Most assessments of PASS protocols and reports will benefit from a multidisciplinary approach, such that PV assessors work in collaboration with assessors with other expertise (e.g. epidemiology, biostatistics, specific clinical expertise and/or senior scientific or regulatory experts in general). Pharmacoepidemiological support is considered valuable and should be available if possible.

Some form of quality assurance is advised, and assessor meetings or peer reviewers may be used to review draft ARs.

Concerning timelines, it is useful to have personal timelines, that take into account time needed for consultation with other assessors and for quality assurance.

4.1.2. Pre-assessment preparatory work

Pre-assessment preparatory work may include consultation of relevant guidelines provided in section 4.2.1 below. Familiarity with the legislation and the EMA guidance on PASS and PAES is recommended in order to be fully aware of the process. A clear understanding of the regulatory history of the medicine, in particular the data and considerations underlying the safety concern(s) being investigated, the pharmacology of the substance, and the clinical particulars of the indication as well as the event of interest, is imperative for good assessment of a PASS.

The template provided by the EMA should be used and contains helpful guiding text.

4.1.3. Comment on assessment reports produced by other Member States

Only a small fraction of NCAs comment on all PASS ARs, so it is proposed that the NCAs establish a method for prioritising which PASS ARs to focus on as MS. The vast majority of agencies prioritise the work based on types of studies, either by selected therapeutic areas or types of procedures.

4.2 Support for overcoming challenges during evaluation of PASS protocol and results

4.2.1 Guidelines, checklists, registries and databases

The EMA template AR gives useful guidance when drafting the report (for links see introduction). There may also be other forms of internal guidance, such as a checklist or Q&A document, within NCAs to help ensure the consistency and quality of the report.

In addition, there are a number of useful and reputable guidelines, checklists registries and databases that could be used when assessing protocol and study results. Links to these guidelines together with the documents are provided in Annex 1.

- The assessor must be familiar with GVP module VIII. GVP: Module VIII – PASS (protocol and study results)
- Additional support could be found in EMA's Question and Answers.
- Many NCAs recommend the use of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) checklist for methodological standards, which provides support when assessing protocols in terms of checking that essential information is provided in the study protocol. This checklist should always be provided with the submission.
- Additionally the ENCePP provides guidance on how to *create* a PASS protocol in the 'ENCePP Guide on Methodological Standards in Pharmacoepidemiology'. This information is useful for a more in-depth reading and several references to practical examples from the literature are provided. Additionally, the guide also provides information regarding pharmacogenetic and vaccine study protocols.
- ENCePP Resources Database comprises the *Inventory of ENCePP research centres and networks,* and the *Registry of EU data sources*. Both the Inventory and the Registry are searchable and allow the identification of centres and data sets by country, type and other relevant criteria. This may be useful for the assessor to identify further relevant EU data sources as needed.

- The EU PAS Register is a publicly available register of non-interventional post-authorisation studies (PAS). PASS initiated, managed or financed by a MAH and required in a RMP are entered into this Register. This may facilitate assessors to identify studies that are relevant to consider while assessing a PASS protocol.Concerning observational studies in general, an international collaborative initiative of epidemiologists, methodologists, statisticians, researchers and journal editors named STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) has presented statements on how to present results from observational studies. While the checklists identify the key elements, the article explains the checklist items, methodological background and published examples of transparent reporting (von Elm et al. PloS 2007) (study results)
- Concerning the use of databases, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) task force has provided a checklist in the form of 27 questions to guide decision makers as they consider the database, the study methodology, and the study conclusions (Motheral et al., 2003) (protocol and study results)
- Additionally, concerning the use of databases, members of the International Society for Pharmacoepidemiology (ISPE) special interest group (SIG) on database research has published guidelines for good database selection and use in pharmacoepidemiology research (Hall et al. 2011). The guidelines include critical questions and comments regarding important issues that have to be illustrated (protocol and study results)
- Recently an international collaboration funded by Canadian Institutes of Health Research, Swiss National Science Foundation and Aarhus University published guidelines, to address reporting items specific to observational studies using routinely collected health data: The REporting of Studies Conducted Using Observational Routinely-Collected Health Data (RECORD) Statement: methods for arriving at consensus and developing reporting guidelines (study results), The collaboration was created as an extension to the STROBE statement.

There are also examples of additional tools that have been created by national authorities supplementary to the EMA templates. An example is the practical guide submitted by the AEMPS during the survey, a guide that also reflects the assessment of risk of promotional aspects of the study (the AEMPS guide can be found in Annex 2). This guide is adapted from the post-authorisation studies guidance of the Spanish Committee for the coordination of the post-authorisation studies.

Additionally, there are challenging questions regarding promotional issues when assessing a PASS protocol. Some MSs have introduced national regulation, which has been shown to be effective in avoiding promotional studies.

Generally, a study should not be an incentive to advise, prescribe, purchase, supply, sell or administer medication and the prescription of the medicine should clearly be separated from the decision to include the patient in the study.

In order to further question an eventual promotional intention, one can check that:

- There is a clearly defined and relevant research question
- The study does not look at issues already addressed
- The study involves a comparator group
- The study does not seem larger than needed to answer the questions proposed
- The study is not loosely supervised regarding safety follow-up

This is supported by the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), which is a global, non-profit, non-governmental organisation with a secretariat based in Geneva, Switzerland. The IFPMA represents the research-based pharmaceutical industry and has proposed a Code of practice and advocates that a clinical study must have a legitimate scientific purpose.

4.2.2 Experiences from PRAC reported by EMA

In August 2015 the EMA presented experience gained from the first imposed PASS protocols discussed at PRAC. In total, 38 protocols for imposed PASS were assessed by PRAC between September 2012 and March 2015. Two of these protocols were rejected for feasibility issues.

The most common issues for discussion were, in additional to objectives, mainly research methods (such as data source/population, study design, variables/outcomes, study size and data analysis); see Figure 1 below.

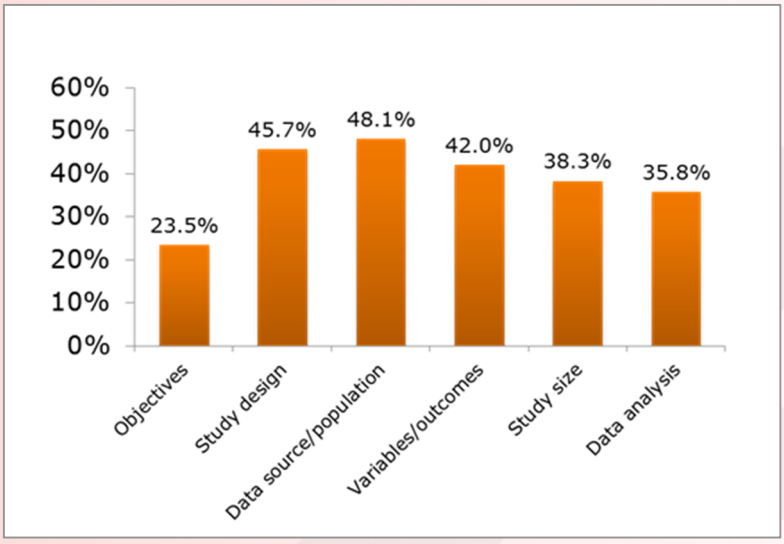

Figure 1: Percentage calculated by dividing the number of times when a methodological issue was raised in the PRAC AR and the total number of procedures employed for protocol assessment and/or endorsement.

This information indicates which areas in protocol assessment generate the highest attention during PRAC discussion, such as data source/population and study design.

It could be mentioned that the issues on study design, setting, data source, variables and size could be related to each other sometimes. The assessor's comment should be placed under the most relevant subheadings in the session of methodology.

The key questions the assessor should keep in mind would be whether the studies will be feasible to generate reliable results sufficiently timely.

4.2.3. Ensuring the quality of the assessment

It could be valuable to have epidemiologists, as well as statisticians, assess whether methodology used by the applicant/MAH in the protocol and study report are appropriate.

The general epidemiology support function could be available routinely, or when it is considered needed.

For imposed studies (category 1), epidemiological input could be obtained from the EMA routinely.

For requested (category 3) studies, the EMA in July 2015 initiated a 12 month pilot to allow MAHs to apply for scientific advice on PASS protocol.

To ensure consistency and quality, comparison with other assessments of similar types of study protocols, for similar products, with similar objectives, is considered valuable.

Collaboration between NCAs should be encouraged in order to share knowledge and lessons learnt.

4.3 Support for drafting requests for supplementary information

The main questions for assessors to consider when assessing the protocol are:

- If the proposed study will provide sufficiently robust scientific evidence to support decisions on regulatory action regarding the underlying safety concerns
- If the proposed study is non-promotional

In order to address these key questions, it is essential to compare how the main objective has been worded in relation to the safety concern, as expressed by the regulators that prompted the PASS. The main objective will then 'drive' the choice of study design, data sources used, sample size, milestones, and other key aspects.

The main objective, as identified by regulators when the need for a PASS was decided, should be the focus during the assessment of the study protocol.

Experience of assessment of final study results of imposed PASS is currently limited, but interpretation of data will involve the critical questions that are raised during the assessment of the protocol. Therefore, the main focus would be to thoroughly assess the protocols.

Annex 1. Guidelines checklists, registries and databases

1. GVP Module VIII Rev 1: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf
2. ENCePP Checklist for study protocol (Revision 2 amended): http://www.encepp.eu/standards_and_guidances/documents/ENCePPChecklistforStudyProtocols.doc
3. ENCePP Guide on Methodological Standards in Pharmacoepidemiology (Revision 4): http://www.encepp.eu/standards_and_guidances/documents/ENCePPGuideofMethStandardsinPE_Rev4.pdf
4. STROBE, von Elm et al. PloS 2007:
   http://strobe-statement.org/index.php?id=available-checklists

   http://www.plosmedicine.org/article/fetchObject.action?uri=info:doi/10.1371/journal.pmed.0040296&representation=PDF
5. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement:
   http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001885
6. ISPOR – A Checklist for Retrospective Database Studies:
   https://www.ispor.org/workpaper/research_practices/A_Checklist_for_Retroactive_Database_Studies-Retrospective_Database_Studies.pdf
7. ISPE's special interest group in database research: Guidelines for good database selection and use in pharmacoepidemiology research:
   http://www.pharmacoepi.org/pub/1c2a306e-2354-d714-5127-9fd12e69fa66
8. ENCePP Resources Database:
   http://www.encepp.eu/encepp/resourcesDatabase.jsp
9. The EU PAS Register
   http://www.encepp.eu/encepp_studies/indexRegister.shtml

Annex 2. The AEMPS Guide

The AEMPS Guide