SCOPE Work Package 8
Lifecycle Pharmacovigilance

PASS
Recommendations

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SCOPE

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Contents

Acknowledgments

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1. Introduction

1.1 Purpose of the document

The purpose of this document is to provide recommendations arising from Work Package 8 (WP8) Lifecycle Pharmacovigilance (PV), Topic 3 Post Authorisation Safety Studies (PASS) assessment. The recommendations cover both assessment of protocols and study reports. The Guideline on good pharmacovigilance practices (GVP) regarding Post Authorisation Efficacy Studies (PAES) is pending and assessment of PAES is not included in this document.

The WP8 lead is Italy (AIFA), and this topic is led by Sweden (MPA) in collaboration with Italy (AIFA), Ireland (HPRA), Spain (AEMPS), Portugal (INFARMED), the United Kingdom (MHRA) and Norway (NOMA).

This document is intended to give recommendations on some aspects of PASS assessment and the drafting of assessment reports. It is not intended in any sense to replace PASS guidance and requirements detailed elsewhere. It is not intended to advise on procedural aspects or to influence templates and guiding text provided by the European Medicines Agency (EMA).

Assessors need to be familiar with legislation and guidelines and to refer to these as appropriate throughout the assessment process.

1.2 Definitions and abbreviations

Terminology	Description
DUS	Drug Utilisation Study
EEA	European Economic Area
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EMA	European Medicines Agency
EU	European Union
GVP	Guideline on good pharmacovigilance practices
ISPE	International Society for Pharmaceutical Engineering
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
MS	Member State
NCA	National Competent Authority
NCE	New Chemical Entity
P	Protocol
PAES	Post Authorisation Efficacy Study
PASS	Post Authorisation Safety Studies
PRAC	Pharmacovigilance Risk Assessment Committee
PV	Pharmacovigilance
R	Results
RECORD	REporting of Studies Conducted Using Observational Routinely-Collected Health Data
RMP	Risk Management Plan
SCOPE	Strengthening Collaboration for Operating Pharmacovigilance in Europe
SIG	Special Interest Group
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
WP	Work Package

1.3 Attachments

Ref no.	Document name
Annex 1	WP8 Practical Guide on PASS Assessment

1.4 Background

The continued benefit/risk assessment of a medicinal product during its lifecycle is a cornerstone for the effective operation of the pharmacovigilance 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 national competent authorities (NCAs) more tools for planning how to further characterise known or potential important risks and how to gather information on gaps in knowledge in specific subpopulations. Such studies are described in the pharmacovigilance plan of the RMP and involve, for example, cohort prospective and retrospective studies, cross-sectional studies, case studies, drug utilisation studies (DUSs), appropriateness studies and prescription patterns studies.

A survey, based on a questionnaire to NCAs concerning experience and practice in assessment of PASS, is the basis for advice on good practice provided in this document.

1.5 Context

Assessors at NCAs are the main targets for these recommendations, but also the lead of assessor teams and administrative lead within the PV area at NCAs are within the target groups.

2. Aims

The overall aim of recommendations is to contribute to practical advice for the assessment of PASS protocols and final results, as well as to good practice with regard to PASS assessment, which has been found challenging for NCAs participating in the Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action.

3. Methodology

3.1 Development

A web-based survey (web tool: SurveyMonkey) was developed in cooperation with all active participants in the WP8, through e-mail, teleconferences and face-to-face meetings. The survey was disseminated to 28 NCAs participating in SCOPE. By survey close, a total of 25 member states (MSs) had provided responses. This represents a high response rate of 90% (Germany, Austria and Luxembourg are not official SCOPE partners).

The following areas were covered by the survey:

- Organisation and processes
- Epidemiologic support function
- Training policy
- Training material recommendation.

3.2 Challenges/limits

One of the challenges in identifying current practice at national level is the fact that not all European NCAs have been participating in the SCOPE project, thus the document only reflects the practice in SCOPE participating countries. Moreover, not all questions included in the WP8 survey obtained the maximum response rate, particularly in areas such as PASS and PAES, where some NCAs have little experience. Differences between MSs with regard to their experiences (e.g. not having experience as the Pharmacovigilance Risk Assessment Committee (PRAC) Rapporteur), as well as their resources and priorities, make it difficult to generalise the results.

Due to the multi-factorial nature of the assessment process, it is not feasible to cover all circumstances and each assessment must be conducted on a case-by-case basis.

4. Recommendations

4.1 Organisation and process

Most assessments of PASS protocols and reports will benefit from a multidisciplinary approach, with PV assessors working in collaboration with assessors with other competences.

Some form of quality assurance is advised and the majority of national authorities use assessor meetings to review draft assessment reports, or use peer reviewers within the agency.

Only a small fraction of national authorities comment on all PASS, so it is proposed that the new chemical entity (NCE) establish a method for prioritising. The vast majority of agencies prioritise the work either based on types of studies, selected therapeutic areas or types of procedures.

4.2 Epidemiologic support function

Pharmacoepidemiology expertise is considered valuable and should be available if possible. Providing this type of scientific support and proposing how such a function could be organised and resourced may be outside of the remit of the SCOPE project.

4.3 Training policy

The mainstay in training is senior PV colleagues acting as mentors, and additional training is most frequently provided on an ad-hoc and individual basis. Only a small number of national authorities mentioned some form of regular training programme for new employees and/or assessors.

Comparison with other study protocols/reports was the most frequently reported method to assist assessment and the vast majority (95%) of the NCAs use GVP Module VIII as a guideline, whilst half of the NCAs use the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) checklist and guideline. Responses suggested that internal documents are developed for national procedures.

4.3.1 Training session on PASS assessment

Within the SCOPE Project, there will be a training session/workshop which specifically relates to the assessment of PASS. The workshop will be an introduction to the hints and tips document with practical examples, and will be lead by experienced assessors.

4.3.2 European Exchange Programme

Within WP8 there is a proposal for an Exchange Programme within the network of medicines regulatory authorities from the 31 European Economic Area (EEA) MSs, the European Commission and the EMA. The exchange of competence, experience and knowledge among assessors from MSs seems a very relevant initiative for the improvement of the effectiveness of the network, especially the work of the PRAC.

It is also foreseen that such a programme will help to:

- Increase the level of competence of PV assessors in Europe
- Ensure the overall quality of pharmacovigilance assessments
- Encourage a more harmonised approach to assessment, the use of new and existing tools and a build-up of competences in NCAs.

4.4 Training material recommendation

4.4.1 Guidelines

There are a number of useful and reputable guidelines and checklists that can be used when assessing protocol (P) and study results (R). These documents can be found in the annex:

- The GVP Module VIII, which is necessary for assessors. GVP: Module VIII – PASS (P) (R)
- Many NCAs recommend the use of the ENCePP checklist for methodological standards, which provides support when assessing protocols in terms of checking that the essential information regarding study protocol is provided (P)
- 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 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 studies (P)
- 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 checklist identifies the key elements, the article explains the checklist items as well as gives methodological background and published examples of transparent reporting (von Elm et al. PloS 2007) (R)

- Concerning the use of databases, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task force has provided a checklist written 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) (P) (R)

- Additionally concerning the use of databases, members of the International Society for Pharmaceutical Engineering's (ISPE) special interest group (SIG) on database research have 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 when evaluating protocols and studies based on healthcare database used in observational research (P) (R)
- Recently, an international collaboration funded by Canadian Institutes of Health Research, Swiss National Science Foundation and Aarhus University published a Guideline. The collaboration was created as an extension to the STROBE statement 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.

4.4.2 Hints and tips from WP8 on PASS assessment

Hints and tips on PASS assessment from WP8 will be part of training material.

4.4.3 PRAC experience from imposed PASS

The PRAC cumulative experience with regard to imposed PASS protocols will be reviewed, and might be part of the training material.

5. Impact assessment (anticipated)

The proposed recommendations are aimed at improving understanding of the different challenges faced by assessors in dealing with PASS assessment. The recommendations should help to ease some of these challenges and enable NCA staff to work more closely to strengthen the European and global PV network. The recommendations will hopefully contribute to ensure that NCAs are able to support the PRAC with high-quality assessment and advice.

Annexes

Annex 1. WP8 Practical Guide on PASS Assessment

WP8 Practical Guide on PASS Assessment