SCOPE Work Package 8
Lifecycle Pharmacovigilance

PSUR/PSUSA and Referral Recommendations

2016

SCOPE

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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) – benefit/risk (B/R) assessment in the context of Periodic Safety Update Report (PSUR) and referral. WP8 lead is Italy (AIFA); this topic is led by Italy (AIFA) in collaboration with Ireland (HPRA), Sweden (MPA), Spain (AEMPS), Portugal (INFARMED), Norway (NOMA), and United Kingdom (MHRA).

The recommendations include key considerations and useful advice for PV assessors, such as practical guides in support of PSUR/ Single assessment of Periodic Safety Update Reports (PSUSA) and referral assessments (Annex 1 and Annex 2).

This document is not intended to replace any existing guidelines, but is written to share experience and useful PV practices identified within the European Union (EU) PV network.

1.2 Definitions and abbreviations

Terminology	Description
ADR	Adverse Drug Reaction
ADS	Alternative Data Source
B/R	Benefit/Risk
DSUR	Development Safety Updated Report
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GVP	Guideline on good pharmacovigilance practices
MS	Member State
NCA	National Competent Authority
PL	Product Lead
PM	Procedure Manager
PRAC	Pharmacovigilance Risk Assessment Committee
PROTECT	Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium
PSUR	Periodic Safety Update Report
PSUSA	Single assessment of Periodic Safety Update Reports
PV	Pharmacovigilance
SCOPE	Strengthening Collaboration for Operating Pharmacovigilance in Europe
SOP	Standard Operating Procedure
WP	Work Package

1.3 Attachments

Ref no.	Document name
Annex 1	WP8 Practical Guide on PSUR-PSUSA
Annex 2	WP8 Practical Guide on Safety-related Referrals

1.4 Background

National Competent Authorities (NCAs) for medicinal products make regulatory decisions based on qualitative and quantitative assessment of the benefits and risks associated with medicinal products. The Benefit/Risk (B/R) assessment is a complex process, which requires the evaluation of quality, preclinical and clinical data submitted by the pharmaceutical company, integrating this to show how the key evidence, uncertainties and conclusions were used to reach a regulatory decision.

Decision making is a multifaceted undertaking and it involves multidisciplinary competences and specific skills. These include knowledge regarding the estimation of the uncertainty in the data and/or difficulties in predicting long-term outcomes in different time horizons; heterogeneity in effects across patient populations; evaluation of robustness of outcomes; ability to handle multiple objectives, data heterogeneity, differences in perspectives and positions, etc.

Other aspects that could make the process challenging for assessors include the need to ensure consistency across assessments, ability to work in a team and to adhere to proposed timeframes, and good coordination with other participants and stakeholders in the process.

Moreover, NCAs, in the context of medicines B/R evaluation, may face different inherent issues that impact on the process. These issues could include resource limitations and/or decisions regarding the best use of resources, managing a wide scope of expectations, finding the right balance between accurately reflecting the scientific evidence and meeting social demands, handling differences in the national legislative requirements, and so on.

1.5 Context

The European medicines regulatory system is based on a network of NCAs from the 31 European Economic Area (EEA) Member States (MSs), the European Commission and the European Medicines Agency (EMA). In such an heterogeneous context, consistency in the assessments, use of new and existing tools for facilitating decision making and building up competences at NCA level, assume particular importance for improving the effectiveness of the PV network as a whole, particularly in relation to post-authorisation evaluations of risks arising from PV and other safety data.

Considering the complexity of some PSUSA and referral procedures, in order to promote a pragmatic, consistent evaluation process, collaboration among NCAs and high-quality support in decision-making performed by the Pharmacovigilance Risk Assessment Committee (PRAC), the work in the Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) WP8 (Lifecycle Pharmacovigilance) B/R assessment in the context of PSUR and Referral procedures, has focused on:

- Identification of areas where PV is operating well (in particular assessment processes) and useful tools to carry out PSUR/PSUSA and referral assessments
- Promotion, description and dissemination of good assessing practices

- Support for assessors in addressing some of the identified challenges through the training tools

The main target population for the recommendations is EU PV assessors.

The recommendations concerning WP8 will be used in the later training package for assessors to promote consistency and support high-quality evaluation of B/R of medicines in the post-marketing setting. It is worth highlighting that promoting a single approach does not mean regulatory decisions among NCAs will be harmonised; conversely, the differences inherent in each agency's processes and regulatory models add value to the EU PV and regulatory network in general, and should be preserved in the decision-making process.

The recommendations complement WP8's recommendations on the use of alternative data sources (ADSs) and on PV assessors' levels of competency.

- The EU Network Training Centre (www.hma.eu/otsg.html) aims to create a European central platform for the exchange of information and supply of regulatory and scientific training across the EU regulatory network.
- The Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) (www.imi-protect.eu/) project introduces innovative approaches to the B/R assessment of medicines. It is a public-private partnership for innovative methodologies in pharmacovigilance and pharmacoepidemiology coordinated by the EMA. The goal of PROTECT is to strengthen the monitoring of the benefits and risks of medicines in Europe by developing innovative methods, such as enhancing early detection and assessment of adverse drug reactions (ADRs) from different data sources (clinical trials, spontaneous reporting and observational studies) and enabling the integration and presentation of data on benefits and risks.
- The 'Strategy for supporting PRAC assessment with best evidence' focuses on the scientific robustness of post-authorisation evidence and on strengthening the evidence underpinning decisions on individual medicines or classes of medicines to increase the quality of advice and the consistency of elements in PRAC assessments (PRAC work plan EMA/PRAC/269153/2015).
- The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) is an EMA-led initiative that brings together expertise and resources in pharmacoepidemiology and PV across Europe (http://www.encepp.eu/index.shtml). ENCePP is aimed at further strengthening the monitoring of the B/R balance of medicinal products by facilitating the conduct of high-quality, multi-centre, independent post-authorisation studies with a focus on observational research.

2. Aims

The overall aim of the WP8 recommendations is to contribute to the development of the competency of PV assessors and other scientific assessors across the EU, in order to support efficient and scientifically robust processes. This document highlights some aspects of the B/R evaluation that can have an important influence on the quality of an assessment. It is intended as a supportive tool to be used in conjunction with the relevant legislation, Guideline on good pharmacovigilance practices (GVP) Module VII, and EMA templates guidance text. It was developed to offer practical guidance to assessors during the PSUR/PSUSA and referral assessment. It is neither intended to provide procedural guidance or scientific guidance, nor to replace any of the existing guidelines.

Moreover, the aims of the recommendations are to create the bases for the training materials for PV assessors (in line with NCA expectations reported in the relevant surveys) and to provide the opportunity for better work-sharing, linkage and cooperation among MSs.

3. Methodology

3.1 Development

The recommendations arose from analysis of the survey results, the internal discussion among contributors to WP8, and global analysis of the overall findings in WP8.

The survey included questions on NCAs' experiences with the assessment of PSUSAs and referrals. With regard to PSUSAs, 10 out of 24 NCAs who responded to the specific survey question indicated that they had experience with this procedure and identified challenges and solutions for the assessment of PSUSAs. The survey responses also identified current practices and helpful tools already used by NCAs for the evaluation of benefits and risks. Promoting the exchange of experiences, successful methods and good operating PV has been highlighted as the most important way to overcome the challenges.

For referral procedures, the survey highlighted that most of those who participated do not have a formal internal document or standard operating procedure (SOP) to provide structured guidance for assessors in the context of referrals. The survey identified many challenges faced by assessors and described the strategies that have been adopted to overcome some of these.

One of the most important inputs detected in the survey was the proposal to develop a practical guidance paper on PSUR/PSUSA and referral assessment.

3.2 Challenges/limits

Due to the differences in the structure and context of NCAs across MSs, not everything in this paper will be applicable or relevant for everyone – nor is it intended to be.

Since not all European NCAs have participated in the SCOPE project, considerations expressed in this paper reflect only the survey feedback and analytical work performed by the participants in WP8. Therefore, not all EU PV experiences or potentially useful materials and sources of information (e.g. practical guidance, SOPs etc.) that might be available are reflected in this document.

4. Recommendations

The recommendations are structured so that they can be considered as general (overall reflections and aspects concerning both procedures – PSUR/PSUSA and referral) and procedure-specific recommendations (practical guidance for assessors).

4.1 General recommendations

4.1.1 "Work in team" strategy and proactivity in communication

This recommendation aims to promote good, efficient and early communication between all involved actors. First of all, effective communication between rapporteur and co-rapporteur(s) appointed for the procedure, EMA Procedure Manager (PM), Product Lead (PL) and MAH(s), and between assessors within the same NCA, should be considered from the beginning of the B/R assessment procedures. Furthermore, during decision-making, it is recommended to consider the views of patients, healthcare professionals and experts over the course of the B/R evaluation of a medicine, whenever considered appropriate.

Assessors should be encouraged to proactively seek advice from experts where relevant and this should be managed in a timely and interactive manner to allow for the smooth progression of the procedure.

The possibility of establishing a dedicated communication office and/or communication officer to effectively manage external expectations and information-sharing is also recommended.

4.1.2 Importance of reviewing

The sharing of opinions and review, in particular for complex and challenging PV assessments, and at different stages of the process, is strongly recommended.

Informed and shared decision-making represents the basis of consistent assessment and regulatory outcomes. Review can be obtained at different levels through the involvement of senior assessors, PRAC members, NCA advisory and scientific quality assurance groups have important roles in achieving high quality assessments and shared positions.

A number of NCAs (n= 10, 83%) reported that working toward the final NCA position on B/R evaluation involved a discussion and agreement of the final recommendation with a dedicated advisory board or working group, or with a scientific quality assurance group.

The sharing of opinions and reviewing by different actors could play an important role in the achievement of high quality assessments and shared positions.

4.1.3 Training and education opportunities for assessors (continuous learning)

Continuous education of PV/clinical assessors is necessary to ensure and support evidence-based B/R assessments. Specific training, including introductory, intermediate and advanced level training modules, is recommended to build up and maintain assessors' levels of competency. Procedure-specific training modules, including different formats (e.g. e- learning, face-to-face interactive training with, for example, PowerPoint presentations, and webinars) will be developed by WP8.

An overview of institutions giving courses of value for PV/clinical assessors in general will be provided by WP8. Additionally, a list of textbooks and scientific papers considered useful for PV/clinical assessors' activities will be provided. Moreover, the benefits that could be obtained by implementing an exchange programme for PV/clinical assessors are addressed in a WP8 concept paper. This paper lays out the possible basis for an EU-wide programme for sharing experience and knowledge among assessors from MSs and explores the possibilities for implementation of the secondment/exchange programme as a tool for improving the effectiveness of the PV network.

4.1.4 Build up internal quality systems (e.g. SOPs, mentoring systems, definitions of the roles, etc.)

In total, 13 of 24 (54%) of the NCAs who responded in the survey have a regular internal quality system (e.g. SOPs, internal guide) for B/R assessment in the context of PSUR assessment with reference to GVP module VII. Although 74% of responders do not have a regular internal quality system for B/R assessment in the context of referral procedures, all assessments are prepared in accordance with current relevant guidelines. NCAs may therefore wish to consider developing and improving local quality systems. This issue has been further addressed in the SCOPE WP7 on quality management systems and some common sessions are foreseen during the SCOPE workshop to promote consistency of quality systems at NCA level.

4.1.5 Promoting use of Alternative Data Sources (ADSs) and improving access to information

The recommendation to the PV network would be to try, as far as possible, to improve access to information useful for B/R evaluation decision-making. During the assessment, the use of relevant and validated data from ADSs (i.e. outside of spontaneous reporting) is recommended. To help this happen in different settings across the EEA (European Economic Area), it is of particular importance that NCAs should consider the utility of ADSs in PV assessments, to collaborate in designing strategies that could support the network to identify more useful data and to fill gaps in information.

In order to support this objective, the deliverables from WP8 will include a catalogue of ADSs recommended by NCAs and the platform for sharing experiences/good practices for the use of ADSs in the context of the PV procedures evaluation. These deliverables will be available on the SCOPE website.

4.2 PV procedure–specific (PSUR/PSUSA and referral) recommendations

In the context of procedure-specific recommendations (please see Annex 1 and Annex 2) consideration is given to the practical approach during evaluation of PSUR/PSUSA and referral assessment, and to the factors that may support consistent assessment, including:

- Planning and organisation of the work
- Overcoming challenges during assessment
- The drafting of assessment reports and, in particular, requests for supplementary information
- Delivery of procedure recommendations, final outcomes and requests for commitments
- Presenting of assessment reports at PRAC

5. Impact assessment (anticipated)

The impact on the EU PV system that would be expected of the proposed work, essentially concerns the opportunity to promote consistency in the B/R evaluation of medicines in the post-marketing setting, and to build up assessors' levels of competency across the EU to support efficient and scientifically robust assessment processes. Recommendations and training materials for assessors will be prepared and translated as a final deliverable from WP8.

Annexes

Annex 1. WP8 Practical Guide on PSUR-PSUSA

WP8 Practical Guide on PSUR-PSUSA

Annex 2. WP8 Practical Guide on Safety-related Referrals

WP8 Practical Guide on Safety-related Re