SCOPE Work Package 8
Lifecycle Pharmacovigilance

Risk Management Plan Recommendations

2016

SCOPE

SCOPE Work Package 8 Lifecycle Pharmacovigilance RMP Recommendations

SCOPE

Contents

Acknowledgments

Authors

Ingebjørg Buajordet, Anja Schiel, Jelena Ivanovic (IT), Leonor Chambel (PT), Jane Woolley (UK), Alison Shaw (UK), Qun-Ying Yue, Karl Mikael Kälkner

Co-authors/contributors

Eleanor Carey (IR), Elena Marotta (IT), Virginia Cuconato (IT), Marco Di Girolamo (IT)

WP8 active participants

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

Ingebjorg Buajordet, Niamh Buckley, Eleanor Carey, Leonor Chambel, Maria Consuelo Cicalese, Virginia Cuconato, Marco Di Girolamo, Yvette Escudero, Rolf Gedeborg, Margarida Guimaraes, Jelena Ivanovic, Karl Mikael Kälkner, Miguel Ángel Macia, Elena Marotta, Ana Martins, Dolores Montero, Gunnar Rimul, Anja Schiel, Eva Segovia, Alison Shaw, Almath Spooner, Annika Wennberg, Jane Woolley, Qun-Ying Yue

1. Introduction

1.1 Purpose of the document

The purpose of this document is to provide recommendations arising from the Work Package 8 (WP8) – Lifecycle pharmacovigilance (PV) topic Risk Management Plan (RMP) assessment. The WP8 lead is Italy (AIFA), and this topic is led by Norway (NOMA) in collaboration with Italy (AIFA), Portugal (INFARMED), United Kingdom (MHRA), and Sweden (MPA).

The recommendations include the main findings, principal conclusions and practical guidance (attached in Annex 1) useful for PV assessments.

1.2 Definitions and abbreviations

Terminology	Description
CMD(h)	Co-ordination group for Mutual recognition and Decentralised procedures (human)
CHMP	Committee for Medicinal Products for Human Use
CP	Centralised Procedure
DCP	Decentralised Procedure
DUS	Drug Utilisation Study
EEA	European Economic Area
EPAR	European Public Assessment Report
EM	Educational material
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GVP	Guideline on good pharmacovigilance practices
ISPE	International Society for Pharmacoepidemiology
MAH	Marketing Authorisation Holder
MRP	Mutual recognition procedure
MS	Member State
NCA	National Competent Authority
PAES	Post Authorisation Efficacy Study
PASS	Post Authorisation Safety Studies

Terminology	Description
PRAC	Pharmacovigilance Risk Assessment Committee
PV	Pharmacovigilance
RMM	Risk Minimisation Measure
RMP	Risk Management Plan
SOP	Standard Operating Procedure
WP	Work Package

1.3 Attachments

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

1.4 Background

The aim of RMP assessment is to develop the best possible picture of the identified and potential risks of the product under assessment, and to identify missing information, ensure that appropriate studies are conducted to gain more knowledge about a product's risks and to ensure that appropriate Risk Minimisation Measures (RMMs) are put in place where necessary.

Based on a survey of existing processes and standards for RMP assessments at national level, the following recommendations regarding current practice have been developed to ensure that national competent authorities (NCAs) are able to support the Pharmacovigilance Risk Assessment Committee (PRAC) with high-quality assessment and advice.

1.5 Context

Assessors at NCAs are the main target audience for these recommendations, as well as leads of assessor teams and administrative leads within the PV area at NCAs.

2. Aims

The overall aim of these recommendations is to contribute practical advice with regard to the assessment of RMPs, as well as good practice in dealing with the parts of RMP assessment that have 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 email, 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
- Assessment of the different parts of the RMP: Safety Specifications, Pharmacovigilance Plan, RMMs, Effectiveness of RMMs, Summary of RMP
- Assessment of updates of RMP
- Training

3.2 Challenges/limits

One of the challenges in identifying current practice at national level is that not all European NCAs have been participating in the SCOPE project, and the document therefore only reflects the practice in SCOPE participating countries. Not all recommendations will apply to all RMPs or all NCAs, which should take from them what suits their organisation.

Another challenge is that part of the RMP assessment procedure has changed since the survey was performed, particularly the way in which safety specifications are assessed. This is reflected in the discussion of practical approaches to the assessment of safety specifications in sections 4.1, 4.2 and 4.3.

During the SCOPE project period there was also an ongoing revision of the Guideline on good pharmacovigilance practices (GVP) Module V Risk Management Plan. Major changes are foreseen that will influence current recommendations. Therefore, these recommendations may need to be updated before the final training module is arranged.

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

PV and/or clinical assessors should be responsible for assessment of the RMP document, but collaboration with pre-clinical assessors is important during the assessment of the safety specifications, and collaboration with experts in (pharmaco)epidemiology/statistics is important when assessing the pharmacovigilance plan.

Establishing assessment teams for the individual procedure is recommended. Responsibilities need to be clearly defined based on the most recent procedures at EU level. For example, new applications in Centralised Procedure (CP) implicates that the safety specifications are to be assessed by the Committee for Medicinal Products for Human Use (CHMP) Rapporteur in the CHMP assessment report and prospective planning including the post-authorisations studies and risk minimisation are to be assessed by the PRAC Rapporteurs.

4.2 Processes

The administrative procedure/process within the individual NCA should be described in a Standard Operating Procedure (SOP). To ensured the best quality of the scientific assessment, mentoring or peer reviewing by skilled assessors and/or senior assessors are of importance. In addition, a 'Hints and Tips' document for guidance on the main aspects to consider during the assessment has been written based on responses given in the survey and further elaborated by representatives of some NCAs.

Interim meetings within the assessment team during the assessment are useful and access to internal or external experts was found to be valuable among most NCAs, regardless of size.

Adherence to timelines is important. Careful work planning and prioritisation are therefore key elements.

The consistency with the RMP for the originator's product or other products with the same substance is considered important. An easy access to RMP assessment reports / summaries is recommended, e.g. for products in central procedure, the European Public Assessment Report (EPAR) will be essential, whilst, for products in Mutual Recognition Procedure (MRP) / Decentralised Procedure (DCP), the publication of summaries of RMPs by the Coordination group for Mutual recognition and Decentralised procedures (human) (CMD(h)) will be useful.

However, once the GVP V is updated (revision ongoing), the revised definition of important risks may result in RMPs with fewer safety concerns listed than has been the practice for existing RMPs for the same active substance (only risks that are considered to be highly relevant to the B/R will be included according to revised guidelines).

4.3 Assessment of the Safety Specifications

One challenge is how to decide if safety issues are important enough to be included in the safety specifications. Another challenge is to decide if the safety issue to be included should be characterised as an identified or as a potential risk. The practical guidance, based on the survey and provided in Annex 1, has focused on these aspects. The document, however, needs to be updated when the ongoing revision of the GVP Module V has been finalised. This should be taken on board when planning the future training session.

4.4 Pharmacovigilance Plan

The challenge of pharmacovigilance planning is to decide whether additional PV activities are needed, what kind of activities are needed, and how to categorise studies that are to be included according to the scale given (category 1-3). The categories are described in the GVP, but the survey has identified that NCAs need further guidance to improve consistency in applying these categories. The ongoing revision of the GVP Module V has introduced changes to this, which need to be taken on board.

Another challenge is the wide spectrum of types of studies: pre-clinical studies, mechanistic studies, pharmacokinetic studies, clinical studies, post-authorisation efficacy studies (PAES) or post-authorisation safety studies (PASS). The survey has identified that many NCAs have little experience with PASS and even less experience with PAES. In addition to the detailed overview of different study designs for PASS given in the GVP Module V, many NCAs find the guidelines by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) or the International Society for Pharmacoepidemiology (ISPE) useful. Useful guidance, based on comments given in the survey, has been included in the 'Hints and Tips' document.

The survey has also identified a need to discuss how thorough the assessment of the synopsis of the proposed studies should be within the RMP assessment, as detailed protocols are to be submitted and assessed later in separate procedures. This is referred to in WP8 Topic 3 on PASS.

The future training session needs to focus on this part of the RMP and to explore practical examples.

4.5 Risk Minimisation Plan

The assessor needs to consider whether there is a need for additional RMMs and what kind of RMMs would be useful. In addition to the more general recommendations given in the GVP Module V, the survey had a question on which factors should be considered of importance in deciding on the need for additional risk minimisation measures. Based on responses to the survey, some useful points to consider have been included in the practical guidance (Annex 1).

Educational material (EM) is the most frequently used tool for risk minimisation and a guidance document has been developed on assessment and handling of these (Addendum 1 to GVP Module XVI). It is recommended to initiate a discussion (e.g. in the form of a workshop) on RMM tools or other forms of risk communication that could be useful in addition to, or as alternative to, the traditional EMs.

4.6 Effectiveness of RMMs

The survey has identified that it is challenging to decide on the best ways of verifying the effectiveness of proposed RMMs. Usually surveys or Drug Utilisation Studies (DUS) are proposed, but the usefulness of these should be discussed, as well as other possible ways of documenting the effectiveness of RMMs.

Specific indicators for measuring the effectiveness of RMMs have not been requested in the survey, but it is recommended to address all of these aspects in training sessions or workshops. A number of studies have been published investigating the effectiveness and usefulness of RMMs. Experiences from this research should also be considered for inclusion in the future training session.

It is also recommended that timelines for when the effect of RMMs can be expected and timelines for testing on the effectiveness should be discussed during the training session.

4.7 RMP updates

Scientifically, there are some challenges concerning assessment of elements that are proposed to be removed from the RMP (removing identified or potential risks). The development of criteria for this within the EU network is recommended. The ongoing revision of the GVP Module V has some new aspects on this that should be included in the future training session and in the “hints and tips” document.

The survey has identified that unnecessary resources are used because a “track changes” version of the updated RMP is not always provided by the marketing authorisation holder (MAH). Clear requirements for the MAHs are recommended during the validation of the variation application.

Other challenges are changes in the Pharmacovigilance Plan, e.g. study updates, new studies proposed and effectiveness of RMMs. Examples would be useful for the future training session.

4.8 Training

Few MSs have specific national training programmes for RMP assessment or for PV assessment in general.

- In-house-training/on-the-job-training under supervision or mentoring of senior assessors was the most frequently mentioned tool for training.
- Lectures/training courses and workshops provided by others (such as the European Medicines Agency (EMA) assessor's training) are used, but to a lesser extent.

Training of assessors must be considered an ongoing necessity due to regular changes in staff and responsibilities and because a general need for the basic training of new assessors in the field has been identified. In addition, a need for ongoing and regularly updated training on new or changing procedures should be provided.

In general, finding suitable training courses is considered challenging. There is therefore a need to help NCAs to identify and set up standardised training programmes for assessors.

Within the SCOPE WP8 topic of Competency, there is an overview of institutions providing courses that will be of value for PV assessors in general. There is also a list of textbooks and scientific papers useful for PV assessors' activities.

4.8.1 Training session

Within the SCOPE Project there will be a training workshop with a separate session dedicated to the assessment of RMPs. The session will include an introduction of the practical guidance (Annex 1) and practical examples (case studies) on the assessment of the different parts of the RMP.

4.8.2 European Exchange Programme

Within the 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 helpful:

- Increasing the level of competence of PV assessors in Europe
- Ensuring the overall quality of PV assessments
- Encouraging a more harmonised approach to assessment, the use of new and existing tools and the build-up of competences in the NCAs
- Improving the ability to refine the results, conclusions and actions taken by competent authorities to guarantee the safety of patients and public health
- Enhancing the level of involvement of rapporteurs/lead MS representatives of different MSs at PRAC by enhancing the level of expertise of their teams of assessors.

It is recommended to support the proposal for developing such a European Exchange Programme.

5. Impact assessment

The proposed recommendations are suggested to lead to improved understanding of the different challenges faced by assessors dealing with RMP assessment. The recommendations should help to ease some of these challenges and enable NCA staff to work more closely, in order 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 RMP Assessment

WP8 Practical Guide
on RMP Assessment