SCOPE Work Package 8 - LIFECYCLE PHARMACOVIGILANCE Executive Summary Report

Authors: Jelena Ivanovic, Anja Schiel, Jane Woolley, Alison Shaw, Marco Di Girolamo, Consuelo Cicalese, Virginia Cuconato, Elena Marotta, Qun-Ying Yue, Karl-Mikael Kälkner, Annika Wennberg, Ingebjørg Buajordet, Eleanor Carey, Niamh Buckley, Margarida Guimarães, Miguel A. Maciá

(Version 4 – June 2015)

1 Introduction

1.1 Purpose of the document

The purpose of this document is to summarize the outcome of WP8 – Life cycle pharmacovigilance survey. WP8 lead IT in collaboration with ES, IE, GR, NL, NO, PT SE and UK.

Within Work Package 8, there are five individual topics:

Topic	Title	Lead	Active Contributors
1	Identification of available data sources outside spontaneous reporting	AIFA (IT)	AEMPS (ES) EOF (GR) HPRA (IE) MEB (NL) NOMA (NO) MPA (SE) MHRA (UK)
2	Risk Management Plan assessments	NOMA (NO)	AEMPS (ES) HPRA (IE) AIFA (IT) MPA (SE) INFARMED (PT) MHRA (UK)
3	Post Authorisation Safety (and Efficacy) Studies protocols and study reports	MPA (SE)	AEMPS (ES) HPRA (IE) AIFA (IT) NOMA (NO) INFARMED (PT) MHRA (UK)
4	Benefit/risk assessment in the context of PSUR and referral procedures	AIFA (IT)	HPRA (IE) MPA (SE) AEMPS (ES) INFARMED (PT) NOMA (NO) (MHRA) UK
5	Competency	AIFA (IT)	HPRA (IE) MHRA (UK)

This report summarizes the main goals, methodology, findings and principal conclusions and recommendations from WP8 survey. More detailed description of WP8 surveys is included in WP8 Topic Specific Survey Reports (see section ***1.4 Attachments***).

1.2 Document Revision History

Version	Revision date	Authors
1	14/03/2015	Jelena Ivanovic, Anja Schiel, Jane Woolley, Alison Shaw, Marco Di Girolamo
2	19/05/2015	Jelena Ivanovic, Anja Schiel, Jane Woolley, Alison Shaw, Marco Di Girolamo, Consuelo Cicalese, Virginia Cuconato, Elena Marotta, Qun-Ying Yue, Ingebjørg Buajordet
3	09/06/2015	Jelena Ivanovic, Anja Schiel, Jane Woolley, Alison Shaw, Marco Di Girolamo, Consuelo Cicalese, Virginia Cuconato, Elena Marotta, Qun-Ying Yue, Karl-Mikael Kälkner, Ingebjørg Buajordet
4	17/06/2015	Jelena Ivanovic, Anja Schiel, Jane Woolley, Alison Shaw, Marco Di Girolamo, Consuelo Cicalese, Virginia Cuconato, Elena Marotta, Qun-Ying Yue, Karl-Mikael Kälkner, Annika Wennberg, Ingebjørg Buajordet, Eleanor Carey, Niamh Buckley, Margarida Guimarães, Miguel A. Maciá

1.3 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
EU	European Union
MS	Member State
NCA	National Competent Authority
PAES	Post Authorisation Efficacy Study
PASS	Post Authorisation Safety Studies
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PSUSA	Single assessment of Periodic Safety Update Reports
PV	Pharmacovigilance
eRMR	Electronic Reaction Monitoring Reports
RMP	Risk Management Plan
SOP	Standard Operating Procedure
WHO	World Health Organization
WP	Work Package

1.4 Attachments

Document name	Authors	Documents
1.4.1 Topic 1 Survey Report Identification of available data sources outside spontaneous reporting	Marotta Elena Ivanovic Jelena Di Girolamo Marco Cuconato Virginia	Topic 1 report.docx **Annex 1 link**
1.4.2 Topic 2 Survey Report Risk Management Plan assessments	Ingebjørg Buajordet Anja Schiel	Topic 2.docx **Annex 2 link**
1.4.3 Topic 3 Survey Report Post Authorisation Safety (and Efficacy) Studies protocols and study reports	KM. Kälkner Q-Y. Yue R. Gedeborg A. Wennberg	Topic 3.docx **Annex 3 link**
1.4.4 Topic 4 Survey Report Benefit/risk assessment in the context of PSUR and referral procedures	Jelena Ivanovic Virginia Cuconato Maria Consuelo Cicalese Elena Marotta Marco Di Girolamo	WP8 Topic 4 Report 22.05.2015.docx **Annex 4 link**
1.4.5 Topic 5 Survey Report Competency	Jelena Ivanovic Marco Di Girolamo	SCOPE WP8 topic 5.docx **Annex 5 link**

1.5 Index

1.6 Background

The legislation on pharmacovigilance that came into force in July 2012 (Regulation (EU) No 1235/2010 and Directive 2010/84/EU[1]) includes a number of provisions to strengthen the post authorization follow up of medicinal products' life cycle. The continued benefit/risk assessment of a medicinal product cycle is a cornerstone for the effective operation of the pharmacovigilance system in the EU.

In areas of health care, including PV, professionals are expected to have attained an appropriate level of competence, that when combined with their past experience and knowledge base, enables them to make decisions and take valid and efficient regulatory actions. Establishment of a more harmonized approach in the assessment and use of the new and existing tools and a build-up of competences in the Member States NCAs to effectively address the examination of benefit-risk of medicines in the context of the main PV procedures (RMP, PASS, PSUR/PSUSA and referral) are needed to improve the ability to refine the results, conclusions and actions taken by NCAs to guarantee the safety of patients and public health.

Marketed medicines can be monitored throughout their whole life cycle with relatively minimal expense and effort. In addition it is beneficial to obtain information on the risks of drugs from a variety of different sources throughout their life-cycle. This data should then be compiled to obtain a comprehensive overview of the benefit/risk profile of a medicine during assessment procedures.

1.7 Context of report

The Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action started in 2013 and will run until 2016. It has been created to support operations of pharmacovigilance in Europe following new requirements introduced by the European pharmacovigilance legislation that came into effect in June 2012. Funded by the Consumers, Health and Food Executive Agency and with contributions from the involved member states, SCOPE will gather information and expertise on how regulators in member states run their national pharmacovigilance systems.

The Joint Action among other tasks is developing a forum for interaction amongst European National Competent Authorities to strengthen regulatory collaboration. This will lead to improved understanding of the different challenges faced by member states. SCOPE seeks a collaborative approach to developing solutions to

[1] Directive 2010/84/EU and Directive 2012/26/EU amending Directive 2001/83/EC, Regulation (EU) No 1235/2010 and Regulation (EU) No 1027/2012 amending Regulation (EC) No 726/2004 and in the Commission Implementing Regulation (EU) No 520/2012. Consolidated versions of the Directive 2001/83/EC and Regulation (EC) No 726/2004 are available in EUR-Lex.

these challenges, enabling national competent authority staff to work more closely together to strengthen the European and global pharmacovigilance network.

2 WP8 Main Goals

Work Package 8 aims to collect information on methods and processes for pharmacovigilance assessments and deliver a report on good practices useful for NCAs in operating pharmacovigilance effectively and to support the PRAC in its work.

A competency framework to support pharmacovigilance for human medicinal products in the benefit/risk assessment throughout the lifecycle will be developed in the context of WP8 topics recommendations.

Appropriate training material will be identified and presented, based on the responses of all NCAs to the surveys and other data/information, to assist NCAs to develop their processes to achieve improved effectiveness and competence.

2.1 Topic 1

The main goal of topic 1 is to produce a status report on the availability and utilization of alternative data sources outside spontaneous reporting amongst NCAs, useful for the benefit/risk assessment procedures in PV context. Useful ADSs are described and characterized in order to provide NCAs with further pharmacovigilance tools to be considered during PV procedures.

2.2 Topic 2

The main goals of topic 2 are to produce a status report on the present organization, processes and methods for assessing RMPs at NCAs, to exchange experience on current methods, core skills and good practices and to develop a training package for assessors.

2.3 Topic 3

The main goals of topic 3 are to produce a status report on the existing methods and processes in NCAs at present, to exchange experience on current methods, core skills and good practices and to develop a training package on assessment of PASS protocol and reports for assessors.

2.4 Topic 4

The main goals of topic 4 are to produce a status report on the methods and processes currently used by assessors in NCAs for assessment of PSUR/PSUSA and

referral procedures, to promote the exchange of experiences, successful methods and good practices. The final deliverable of this work is a recommendation to be used in the later training package for assessors to encourage/promote consistency in evaluation of B/R of medicines in post-marketing setting.

2.5 Topic 5

The main goals of topic 5 are to produce a status report on the existing competency levels and organizational matters in NCAs at present, to exchange experience on core skills and good practices including list of useful trainings and literature. These aspects will be promoted through a WP8 training package for assessors in order to further improve the quality, consistency and efficiency of the work of the European PV Network.

3 Methodology

3.1 Tool and survey method

The questions for the web-based survey were developed in co-operation with all active participants in the WP 8 through e-mail and teleconferences, face-to-face meetings and an introductory survey (details of this survey are available in a separate rapport). The introductory/pilot survey was conducted with the same web tool (Survey Monkey) in order to test the functionality of the survey tool and to detect possible structural problems relative to quality, length and understanding of questions (survey language, question interpretation consistency, logical question sequencing, survey "look and feel"). Tool performance, in particular for survey distribution and data collection was tested as well. For the topics 1, 4 and 5 external validation of questionnaire was obtained by sharing of the pilot questionnaires with WHO representatives.

After adjusting of topics questionnaires in accordance with findings from the pilot survey, the final WP8 topics surveys were conducted from 4 July to 30 September 2014 (the first deadline). E-mail reminders were sent on 29th July, 26 August and 22nd September 2014. The initial deadline was extended by two weeks from 30th September to 15th October 2014 and again to 3rd November 2014 due to an initial slow response. However, by survey close a total of 25 member states had provided responses to all five surveys, with the majority responding in August and September. This represents a high response rate of 90% (Germany, Austria and Luxembourg are not official SCOPE partners). No background information was available through the introductory survey for 4 NCAs of responders to the final WP8 surveys.

A web-based survey method (SurveyMonkey) was chosen for its ease and efficiency. It allows conducting the survey directly via web without additional

specific software requirements. In addition, the tool permits to browse individual responses, to create custom charts, to use filters to focus on specific data views and segments and to easily download the results in multiple formats (e.g. Excel spreadsheet etc.) in order to facilitate the creation of the final reports.

3.2 Setting and participants

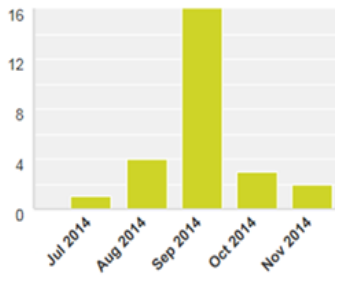
Information about responses

Surveys were disseminated for compilation to 28 NCAs participating in SCOPE. This list of participant contact points was obtained from SCOPE project contact list which was previously established in WP2. Reminders to NCAs who hadn't responded were sent on dates 29 July 2014, 9 September 2014 and 22 September 2014. In order to further increase the replay rates the deadline for replying was extended to the first week of November 2014 when some additional responses returned and the survey was officially closed.

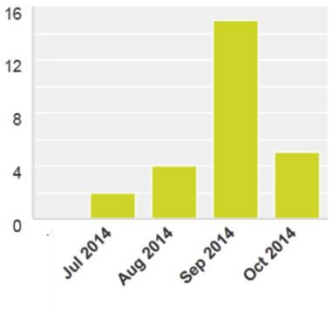
25 of the 28 possible NCAs completed the survey. Cyprus and Iceland did not respond. France sent a partially filled survey for Topic 3 (less than 25% of the questions answered) which was included in the analysis. Two incomplete (<2%) 'Ghost' entries (one for Topic 2 and one for the combined Topic1_4_5 survey) were removed from the analysis as the NCA in question provided a completed survey in addition.

Figure 1. Response rate per month during the surveys:

1a) Topic 1-4-5



1b) Topic 2



1a) Topic 3

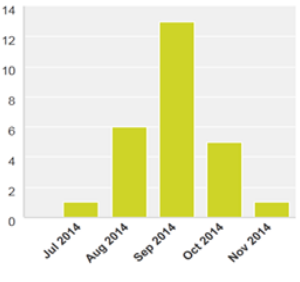
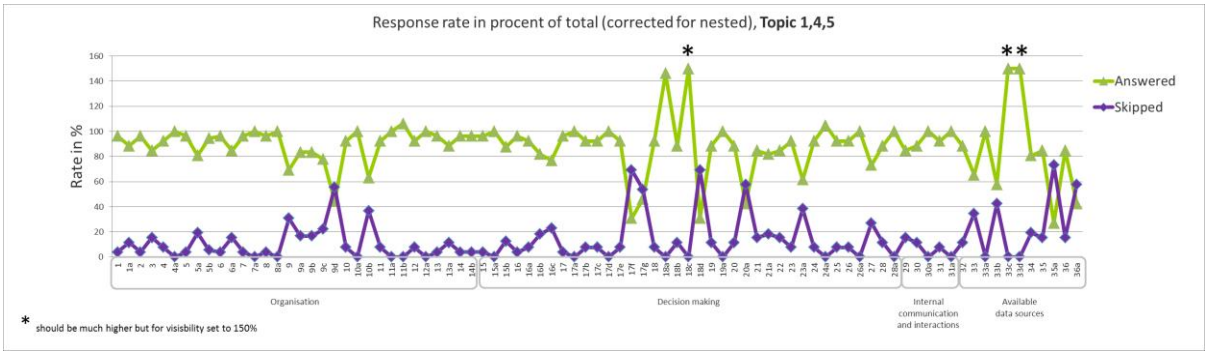
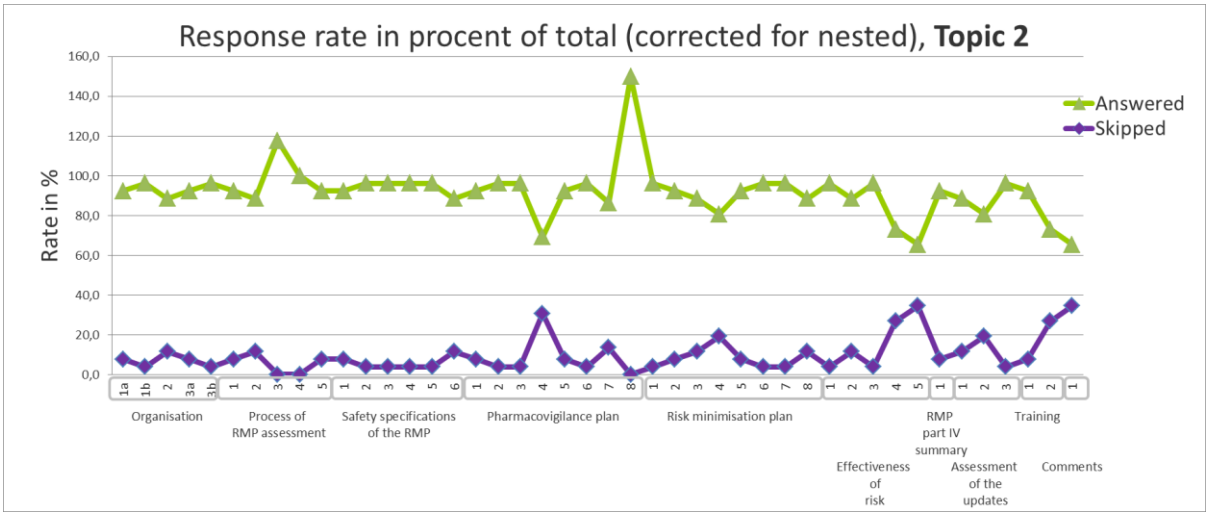


Figure 2. Response rate per questions during the surveys:

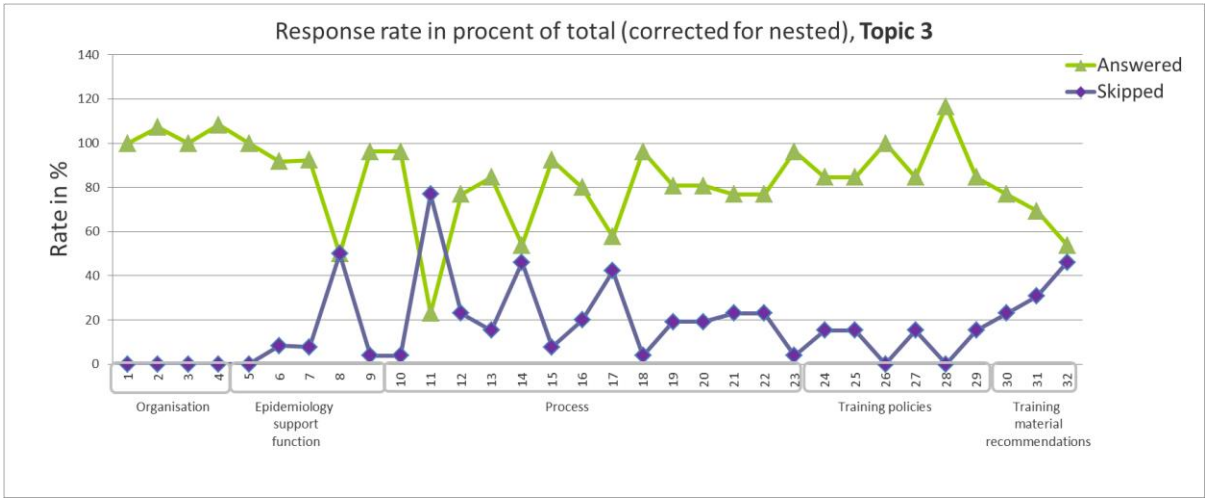
2a) Topic 1-4-5



2b) Topic 2



2c) Topic 3



2d) Response rate in percent of total (corrected for nested), all topics 

Question_identification_doc_link

Main characteristics of MSs/NCAs who participated in the survey

NCAs vary substantially in how long they have been established, ranging from 5 years to 105 years with the majority (57%) existing for less than 20 years **Table 1.**

Table 1. Number of years NCAs have been established

Establishment of NCA (yrs)	N	%
<10	5	22
11-20	8	35
21-30	3	13
31-40	2	9
41-50	1	4
51-100	3	13
>100	1	4

The total number of staff working in NCAs varies substantially between member states, from 18 to 1250 , with 65% of NCAs employing in total between 100 and 400 people (median 201-300). Of these, the proportion of staff working solely in pharmacovigilance varies between 0% and 10%, rising to a maximum of 14% when considering how many staff work on pharmacovigilance activities at any time. Only 2 (9%) of member states who responded currently employ more than 8% of staff for the sole purpose of Pharmacovigilance.

There did not appear to be any obvious correlation between size of Agency and proportion of staff working on pharmacovigilance activities.

Although 91% of respondents reported that a single unit or department is responsible for Pharmacovigilance within their institution, how pharmacovigilance assessors and pharmacovigilance inspectors are organised varies greatly between member states. Nevertheless, the majority are based either in the same department (25%) or in different departments within the same organisation (21%) and all pharmacovigilance activities are conducted in–house by more than 74% of member states.

All but one of the respondents include the following pharmacovigilance activities within their institution's responsibilities: RMP assessment, PSUR assessment, referral assessment, evaluation of PASS protocols. For 7 of the respondents (30%), referral assessment takes place within specialised groups or units within the institution. Whereas RMP, PSUR and PASS protocol assessment takes place within specialised groups or units in 9 of the respondents (39%).

3.3 Data analysis

The results of the 3 different surveys will be summarized by descriptive statistics only. Responses are reported as crude response percentages based on the number of responders. Multiple answers were allowed unless the only options were yes/no. The response percent of the individual answer options therefore do not necessarily add up to 100%. Some questions were designed to be dependent on the response to a previous question (nested) and the reported percentages then refer to the number of responders to that question. In the main rapport figures and tables will be provided for selected key questions only. Where appropriate, questions that belong to the same thematic cluster will be summarized in tabular or textual form. For questions where free-text comments could be given as well as questions based on free-text only the following strategy for analysis was chosen. If possible the textual information will be summarized in the following order:

- Keywords, data is then presented by frequency of occurrence
- logical categories, text is analysed and then assigned to predefined thematic group (example: apple, orange -> assigned to category 'fruit'), categories are then presented by frequency
- If neither of above could be applied the information will be summarized in a textual way.

3.4 Challenges/limits

Among the challenges that could influence the interpretation of the survey results is the fact that not all European NCAs have been participating in SCOPE project, thus figures reported in the reports reflect the current situation in SCOPE participating countries. Moreover, not for all questions included in the WP8 survey was obtained the maximum replaying rate (see Figure 2). Some areas of limited information from NCAs have been identified in the survey (see Figure 2).

Also, the potentially different interpretation of terminology and/or survey questions and the fact that it was decided to not have a questionnaire with compulsory questions may influence the possibility to fully correlate obtained answers. It means that the analysis of some responses reflects only what was specified in the survey by different NCAs (in format of free text) and it could cause that some aspects/responses haven't been reported because reputed obvious, forgotten or for some other reasons (e.g. when degree level and/or high level knowledge of English, are not reported by all NCAs as compulsory for assessors' professional profile).

In addition, the national specific contexts, for example the direct experience or not in some PV procedures , the responsibilities of the authorities as well as resources and priorities may induce uncertainties in generalization of the results.

4 Results

All results from WP8 Topics survey are reported in Topic specific reports (see section ***1.4 Attachments***)

5 Conclusions

5.1 Topic 1

The majority of NCAs (70%) regularly use alternative data sources during benefit/risk assessment procedures, and a long list of ADS, including published scientific literature and databases to registries, have been identified and includes limited and open access data sources. In particular registries and databases, are considered by member states to be of national utility because they are based on population exposed or prescription/consumption data.

The standard Pharmacovigilance tools managed by WHO (Vigibase and Vigimine) and EMA (Eudravigilance, eRMR, etc.) and both pre and post authorization data from MAHs, (DSURs and PSURs, PASS/PAES), are also often consulted during a benefit/risk assessment procedures.

Alternative modalities of reporting are considered useful for detecting new ADRs, serious ADRs with low frequency and interactions previously not studied.

The selection of which ADSs to use during a benefit/risk assessment is most commonly based on its ease of accessibility and the possibility to analyze a large population exposed, together with the applicability of the data to the questions being explored in the assessment Literature consultation is confirmed as the most frequently used data source for the above mentioned purposes, together with data from clinical trials and clinical practice (e.g. guidelines, or general practitioners databases).

5.2 Topic 2

The survey reflects the current practice of assessment of RMPs with focus on aspects identified as challenges and possible solutions. Limitation in human resources has been identified as the major challenge. Competent assessors are key elements and a well organised system, at national and European level, providing continuous training of assessors is considered essential. Easy access to experts that can be consulted during the assessment procedure is of importance.

The GVP Module V is used as the basic guidance for the scientific assessment of RMPs in addition to guiding text in the assessment report templates. The survey has helped to identified useful hints and tips for the scientific assessment of the different parts of the RMP. These will be the basis for further work on a Hints and Tips document.

The survey has also identified some areas where more guidance is needed e.g. how to decide on what risks are important enough to be included in the safety specifications. Criteria for removing safety concerns (and additional RMMs) from the RMP during the products lifecycle should be developed within the European network.

Some areas are more challenging as there is little experience so far, e.g. assessment of the need for PAES or the evaluation of study designs to test the effectiveness of additional RMMs. Based on the information collected in the survey recommendations can be provided for the planning of training of assessors. Not all the suggested solutions to challenges will be suitable for all member states. However, providing a list of possible options may give NCAs some ideas on how to overcome challenges. These areas should be covered in the training programme.

5.3 Topic 3

The results of the survey describe a diversified picture where some NCAs have organized the procedures around the PASS assessment whereas other NCAs have not all components in terms of SOPs, checklists, regular training and all competences in place.

Present methods and processes in NCAs for the assessment of PASS protocol

Out of 25 responders, 21 (84%) reported that they have experience in evaluating PASS protocols.

Many NCAs consider joint assessment to be important for evaluating PASS and pharmacovigilance assessors in collaboration with other competences, such as clinical and pharmaco-epidemiology assessors are the main resources used.

About half of the national authorities have access to epidemiologic support function but 20/24 (83%) reported that a general epidemiological support function should be available.

In total, 15/25 (60%) of the NCAs have some form of a Quality System which most commonly includes assessors meeting to discuss a draft assessment report. The national Quality Systems were described in SOPs according to the comments.

The opinion on time tables was basically divided in those 14 who generally accept them and the 5 who commented that the time tables were too short especially for MS to comment. Several ways exist to support the assessor to adhere to time lines and several methods involve internal deadlines and reminders, particularly for imposed PASS.

Methods for the prioritisation and evaluation of PASS protocols

The approaches for the prioritisation and evaluation of PASS protocols and reports varied among the NCAs. Only 4 NCAs state that they try to comment all PASS protocols and the remaining NCAs have some form of prioritisation to select when to comment. Different aspects for prioritisation were mentioned, for example if the PASS were conducted nationally, if the PASS was imposed or the availability of expertise.

Description of best practice and core skills required for successful evaluation

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 and half of the NCAs use EnCEPP's checklist and guideline. Comments were made that internal documents were developed for national procedures.

The mainstay in training is senior pharmacovigilance 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 program for new employees and/or assessors. The most reported challenges identified by the NCAs were complex study designs followed by the assessment of feasibility and promotional aspects.

The NCA's experiences for specific assessors training

The national authorities have during the survey identified several training programs and provided details of the courses and comments regarding suitability. Summarized in Annex II of WP8 Topic 5.

5.4 Topic 4

5.4.1 Organization and practices for the B/R evaluation

The most commonly reported tools or methods included templates/guidance text, checklists and "hints and tips" documents. The use of templates/guidance text is helpful in order to harmonize evaluation criteria and to provide a summary of the most important results emerging from assessment, while the checklists are helpful especially for junior assessors to support them in the assessment procedure - acting as reminders and confirmation tool for ensuring the completeness of the assessment report. Internal deadlines, reminders at set time points and prioritization have been identified as the most useful organizational practices to deliver assessment reports and other relevant documents according to timelines.

Generally, it appears that meetings, TC and close collaboration among NCA's assessment team and EMA could further improve the consistency of the assessment.

A coordinator at national level could have a key linking role in this process, together with EMA PM and PA.

Regarding to the publication of information and interaction between NCAs and citizens, patients and health professionals, the possibility to organize a dedicated office or to have dedicated Press officer in each NCA could be useful for the successful management of external expectations and reputational risk.

Concerning submission requirements for the PSUR cycle to be reported in EURD list in total 21 of 24 NCAs, (87%) considers different factors when assessing these requirements. The attention is particularly focused on products with limited safety information available and on situations where numerous and/or significant signals emerged for the medicinal product.

Half of NCAs regularly or sometimes seek advice from advisory board or working group for achievement of the final NCA's position on B/R evaluation in PSUR.
With regard to the referral assessment procedure, most participating NCAs (74%) do not have a formal internal guide (e.g. SOP) which provides the more structured guidance for assessors. The availability of further tools for facilitation of the assessment (e.g. common guidelines/ checklists/"hint and tips" documents) was considered beneficial by NCAs.

5.4.2 The useful tools to successfully carry out B/R assessments

Two NCA provided a specific tools easily adopted in routine practice as a guidance document to facilitate decisions concerning assessment of the B/R balance that could be considered useful in particular for less experienced assessors:

- A checklist providing the simple and clear instructions to be followed during the assessment process.
- A "hints and tips" document as a guidance to facilitate programming and organisation of the work in the context of referrals.

In addition, positive effects of planning and "brain storming" meetings, EMA templates and internal "questions and answers" process for B/R assessment in PSUR/PSUSA and referral procedures have been identified in the survey.

5.4.3 Identification of challenging aspects in B/R assessment of PSUR/PSUSA and referrals

A number of challenges during the PSUR/PSUSA and referral procedures and possible solutions have been identified by NCAs with experience in that field of PV. The full list of the identified challenges and solutions is provided in the Annex 2 of the Topic 4 report.
Tackling the challenging situations identified by NCAs in the survey with respect to PSURs/PSUSAs and referrals could guarantee that the SCOPE trainings actually address the needs of NCAs.

5.5 Topic 5

5.5.1 Competency levels and types of organization

Most NCAs consider joint/team assessment as essential for evaluating B/R in PV procedures and PV assessors in collaboration with other competences are the main resource.
The engagement of external experts for B/R assessment in the context of different PV procedures is an adopted practice among different NCAs in Europe. Therefore, the appropriate selection process and management of expert databases could play an important role in achievement of the specific expertise. With regard to this issue, practices adopted in some NCAs were identified in the survey.

Almost all NCAs have a quality system in place (e.g. mentoring system, introduction program , obligatory trainings and/or sharing of experiences opportunities) aimed to ensure a good level of expertise for newly employed assessors. In most NCAs a formal training program exists and is updated annually. In addition "On-the-job training" and formal training (with internal or external provider) for both technical/scientific and regulatory knowledge have been recognized by NCAs as the principle methods of ensuring that assessors knowledge is kept up to date .
The exchange program for assessors was recognized by all NCAs as a valuable tool for the promotion of close collaboration, exchange of information and harmonization of effective standards for PV procedures evaluation (assessments).

5.5.2 Core assessor skills required for PV procedures assessment

The heterogeneity of requirements for assessors' professional profile is one of the principal characteristics of the system which has emerged from the survey.
However, the most commonly reported criteria for Junior assessor professional profile reported in the survey are:

- university degree in biomedical sciences,
- working experience in specific field,
- high level knowledge of English
- ability to work in a team,
- ability to manage own workload and to adhere to proposed timelines,
- ability to perform critical analysis of scientific research findings and literature,
- basic knowledge of regulatory procedures,
- adequate knowledge and use of computer applications,
- obligatory training (including on the job training).

Two detailed descriptions of NCAs approaches for definition of skills and compulsory knowledge, experience and expertise for a Junior Assessors have been identified in the survey and could be helpful for other NCAs, if necessary.
Few replies on the compulsory expertise and experience level for Senior Assessor were received. Two examples of criteria for definition of a Senior Assessor profile were identified in the survey that could help NCAs to address this issue if necessary.

5.5.3 Training courses and literature recommended by NCAs as useful for promotion of PV procedures assessment practices

The existence of trainings with different aims and levels at national and international (EU) level, provides a comprehensive, accessible training framework for different types of assessors.

6 Preliminary Recommendations

This recommendations come out from the analysis of the WP8 topics survey data.
Further elaboration of preliminary recommendations is foreseen in the next moths in order to provide the final recommendation for theWP8.

6.1 Topic 1

This report provides an overview of the availability, utility and value of Alternative Data Sources across European NCAs.
The report is focused on delivering recommendation regarding the most useful ADSs to be considered during a benefit/risk assessment of a medicine. An effort has been made to identify and characterize the most appropriate ADS available in European NCAs in order to share and try to have a common approach regarding their use.
A particular section has been dedicated to the useful experience, described in ES, IT and UK, that have been received in the survey regarding their consolidated practice with ADSs.
Additionally, a list of ADSs with a detailed description of their applicability and main characteristics will be developed and promoted in the WP 8 training.

6.2 Topic 2

6.2.1 Organisation

Pharmacovigilance or clinical assessors should mainly be responsible for assessment of the RMP document. Responsibilities need to be clearly defined based on the most recent procedures at EU level. Collaboration with pre-clinical assessor and experts in (pharmaco)epidemiology/statistics is of importance during the assessment of the Safety Specifications and of the Pharmacovigilance Plan. Establishing assessment teams for individual procedures is recommended.

6.2.2 Processes

Scientific assessment is the most important part of the assessment. This is best ensured by access to skilled assessors and/or senior assessors. In addition some MSs have set up useful lists of “hints and tips” for guidance on main aspects to consider during the assessment. Meetings within the assessment team during the assessment are useful and access to experts internal or external is found to be valuable among most NCAs of all sizes.
Adherence to timelines is very important. Key elements to cope with timelines are the availability of competent assessors that can work quickly and autonomously. However, this may be supplemented by prioritization of work and over-time work during the procedures. Support from administrative leaders for solutions to get the time needed is of importance as well as help from coordinators within the NCA.
The consistency of the RMP with the originator or other products with the same substance is important issue. Of importance is therefore an easy access to summaries of RMPs or generic RMPs that are previously approved

6.2.3. Assessment of the Safety Specifications

The scientific assessment itself cannot be described in SOPs, but aspects to consider might be described in guiding documents or "hints and tips" documents. One challenge is how to decide if safety issues are important enough to be included in the safety specifications (of importance for the B/R of the product). Another challenge is to decide if the safety issue to be included should be characterised as an identified or as a potential risk. A draft of "hits and tips" document can be proposed based on the survey, but needs further development e.g. during the future training session.

Consistency in safety specifications between products with the same substance or between products of substances in same pharmacological class is of importance. A system by NCAs for easy access to other RMP assessment reports is recommended.

6.2.4 . Pharmacovigilance Plan

The challenges are to decide if additional pharmacovigilance activities are needed, which activities are needed and how to categorise studies to be included (category 1-4). The categories are described in the GVP, but the survey has identified that NCAs need further guidance for improved consistency in deciding on categories.

Another challenge is the wide spectrum of types of studies: pre-clinical studies, mechanistic studies, pharmacokinetic studies, clinical studies/PAES or 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, the guidelines by ENCePP or ISPE is found useful. Based on comments given in the survey some useful "hits and tips" can be put together.

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, refer to WP8 topic 3 PASS.

6.2.5. Risk minimisation Plan

The important part is for the assessor to consider if there is a need for additional risk minimisation measures (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 factors to be useful for consideration by the assessor. Based on the responses in the survey some "hints and tips" can be recommended.

Educational material (EM) is the most used tool for risk minimisation and several guidance documents have been developed on assessment and handling of these. One recommendation is to initiate a discussion (f.e. in 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.

6.2.6 Effectiveness of RMMs

The survey has identified that a challenge is to decide on best ways of documenting the effectiveness of proposed RMMs. Usually surveys or DUS are proposed but the usefulness of these should be discussed,as well as other possible ways of

documenting the usefulness. 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 as well.
Timelines for when the effect of RMMs can be expected and timelines for testing on the effectiveness is also recommended to be discussed during the training session.

6.2.7. Re-assessment of RMPs

The survey has identified that un-necessary resources are used because track changes are missing. Clear requirements to the MAHs are recommended. Scientifically there is some challenge 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.
Other challenges are changes in the Pharmacovigilance Plan and effectiveness of RMMs. Training and worksharing is recommended to be helpful.

6.3 Topic 3

It is proposed that an effort is made to further characterize the methods to evaluate PASS protocol used in the MSs and focusing on a couple of MSs that have specified their methods in order to further exemplify how to manage PASS protocol assessments.
Secondly, also identify a couple of MSs that are in the process of building a functional procedure and describe the challenges in order to identify relevant issues to focus on during the creation of a working process.
Additionally it is proposed to further analyse the use of checklists with respect to carrying out quality assurance of both the administrative process and the scientific assessment. Those MSs that have reported the use of checklists should be asked to provide a copy of the checklist.
A future collaboration is foreseen between NCA's who have come far in the journey of PASS assessment and NCA's who just start their journey, perhaps in terms of alliances between NCA's.
Future areas to consider may also include e.g. central epidemiological advisory service and storage of PASS.
A list of training courses could be considered.

6.4 Topic 4

The recommendation for topic 4 is complementary with recommendations for WP8 topic 5 that concern PV assessors' competency.

6.4.1 Description of NCAs current practices for the B/Revaluation

- Implementation of internal deadlines, reminders at set time points could be recommended as the most useful organizational practices to deliver assessment reports and other relevant documents according to timelines;

- Communication via TCs and close collaboration among NCA's assessment team and EMA are recommended in order to further improve the consistency of the assessment. Establishment/identification of a coordinator at national level could have a key linking role in this process, together with EMA PM and PA;
- The use of templates' guidance text is recommended because it is helpful in order to harmonize evaluation criteria and to provide a summary of the most important results emerging from assessment;
- The use of checklists is recommended because they are helpful especially for junior assessors to support them in the assessment procedure - acting as reminders and confirmation tool for ensuring the completeness of the assessment report;
- Implementation of a formal internal guide (e.g. SOP) which provides the more structured guidance for assessors is strongly encouraged;
- The possibility to organize a dedicated office or to have dedicated Press officer in each NCA is strongly encouraged in order to facilitate the management of external expectations and reputational risk;

6.4.2 Identification of challenging aspects in B/R assessment of PSUR/PSUSA and referrals and the useful tools to successfully carry out B/R assessments:

- Possible challenging points in the context of evaluation of PSUR/PSUSA and referrals were identified in the survey, thus further training on these issues is recommended. WP8 will develop appropriate training in order to promote the discussion, find possible solutions and give advice on these challenges.
- Positive effects of planning and "brain storming" meetings and internal "questions and answers" process for B/R assessment in PSUR/PSUSA and referral procedures have been identified and it could be recommended for NCAs to evaluate introduction of these methods routinely.
- A checklist providing the simple and clear instructions to be followed during the B/R assessment process will be developed in WP8 and promoted in WP8 training program.
- A "hints and tips" document as a guidance to facilitate programming and organisation of the work in the context of referrals and PSUR/PSUSA will be developed in WP8 and promoted in WP8 training program.

6.5 Topic 5

The recommendations for topic 5 is complementary with recommendation for WP8 topics 2,3 and 4 that concern PV procedure specific competency (RMP, PASS, PSUR/PSUSA and referral procedure assessment).

6.5.1 Competency levels and types of organization

- Collaboration with quality, pre-clinical, clinical assessor and experts in (pharmaco) epidemiology/statistics is of importance during the assessment of the specific PV procedures. Establishing assessment teams for assessment in the context of the specific PV procedures is encouraged.
- Implementation of quality systems (e.g. SOPs describing evaluation process for main PV procedures, assessor professional profile, training programme) aimed to ensure a good level of assessment is recommended.
- The appropriate selection process could play an important role in ensuring of the specific expertise in the context of PV procedures assessment, thus external experts selection process thought use of specific dedicated databases is encouraged.
- Beside the specific expertise which is warranted in the selection of experts, some additional criteria could be pointed-out as useful:

    - possess or develop a working knowledge and understanding of the national/European medicines regulatory procedures;
    - to be able and prepared to speak on a range of relevant issues and not just on their own areas of specialty;
    - to be able to operate effectively on a national expert scientific committee;
    - to be skilled communicators;
    - to be able to assimilate complex scientific information at short notice;
    - to be recognized by their peers and/or be Fellows of the relevant academia institutions;
    - to have a track record of achievement in their specialty.

6.5.2 Core assessor skills required for PV procedures assessment

- Some important characteristics necessary for assessor professional profile could be recommended:
    - university degree in biomedical sciences;
    - working experience in specific field;
    - high level knowledge of English;
    - ability to work in a team;
    - ability to manage own workload and to adhere to proposed timelines;
    - ability to perform critical analysis of scientific research findings and literature;
    - basic knowledge of regulatory procedures;
    - adequate knowledge and use of computer applications;
    - obligatory training (including on the job training).

- Implementation of quality system (e.g. mentoring system, introduction program , obligatory trainings) aimed to ensure a good level of expertise for newly employed assessors and for maintenance of assessors' appropriate level of knowledge is recommended.

- Implementation of continuing professional development programmes, personal educational forms (a format that allows recording of attended trainings) are encouraged for the motivation of assessors' participation in training events.
- The exchange program for assessors as a valuable tool for the promotion of close collaboration, exchange of information and harmonization of effective standards for PV procedures evaluation (assessments) could be encouraged on EU level.

6.5.3 Training courses and literature recommended by NCAs as useful for promotion of PV procedures assessment practices

- On the basis of NCAs input, a list of recommended trainings and literature useful for PV assessors was created and is recommended for continues education of PV assessors. The complete lists of useful trainings and literature are included in Annexes 2 and 3 of WP8 Topic 5 Report.