

# SCOPE Joint Action Work Package 8



## **Strengthening capabilities for benefit risk assessment**

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London



# Benefit /Risk assessment in PV SCOPE

- Ensuring that regulators can respond to emerging or urgent health issues in a **timely and efficient way** is a **key deliverable** of the pharmacovigilance (PV) legislation.
- The individual **Member States (MS)** of the EEA **power the entire PV system** and **provide much of the resource and knowledge** for assessing safety issues.
- The updating of the medicines B/R profiles throughout the lifecycle represents **one of the most challenging and** at the same time **most important tasks** of the PV system.



# Maximising B/R Assessment in PV



- There is a need for an **increase in collaboration among stakeholders**:
  - ✓ to augment **the provision of data to accurately weigh the evolving B/R balance** and to enhance review capability
  - ✓ challenges to accrue information on a medicine's benefits after approval
  - ✓ PM benefit-risk evaluation is mainly influenced by additional safety information

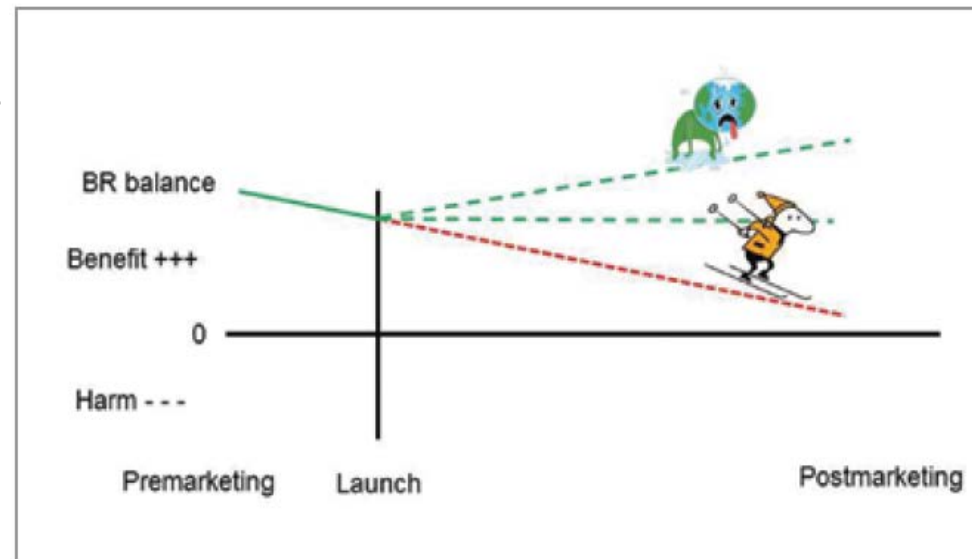
- **Expectations on regulatory Authorities**

Why and how did we make decisions?

Have we been consistent?

Why is it sometimes different from what is expected?

What is the evidence for regulatory decisions?



*B/R assessment in the post-approval period;  
CIRS Workshop report, 12-13 June 2014*

# European Union's new pharmacovigilance legislation



- The importance of **consistency** – **structured, sustainable and systematic process** is fundamental in assisting and improving decision making and facilitates communication.
- Each National Competent Authority (NCA) may come from a different perspective but a consistency in a B/R assessment is of particular importance for the EU PV network.



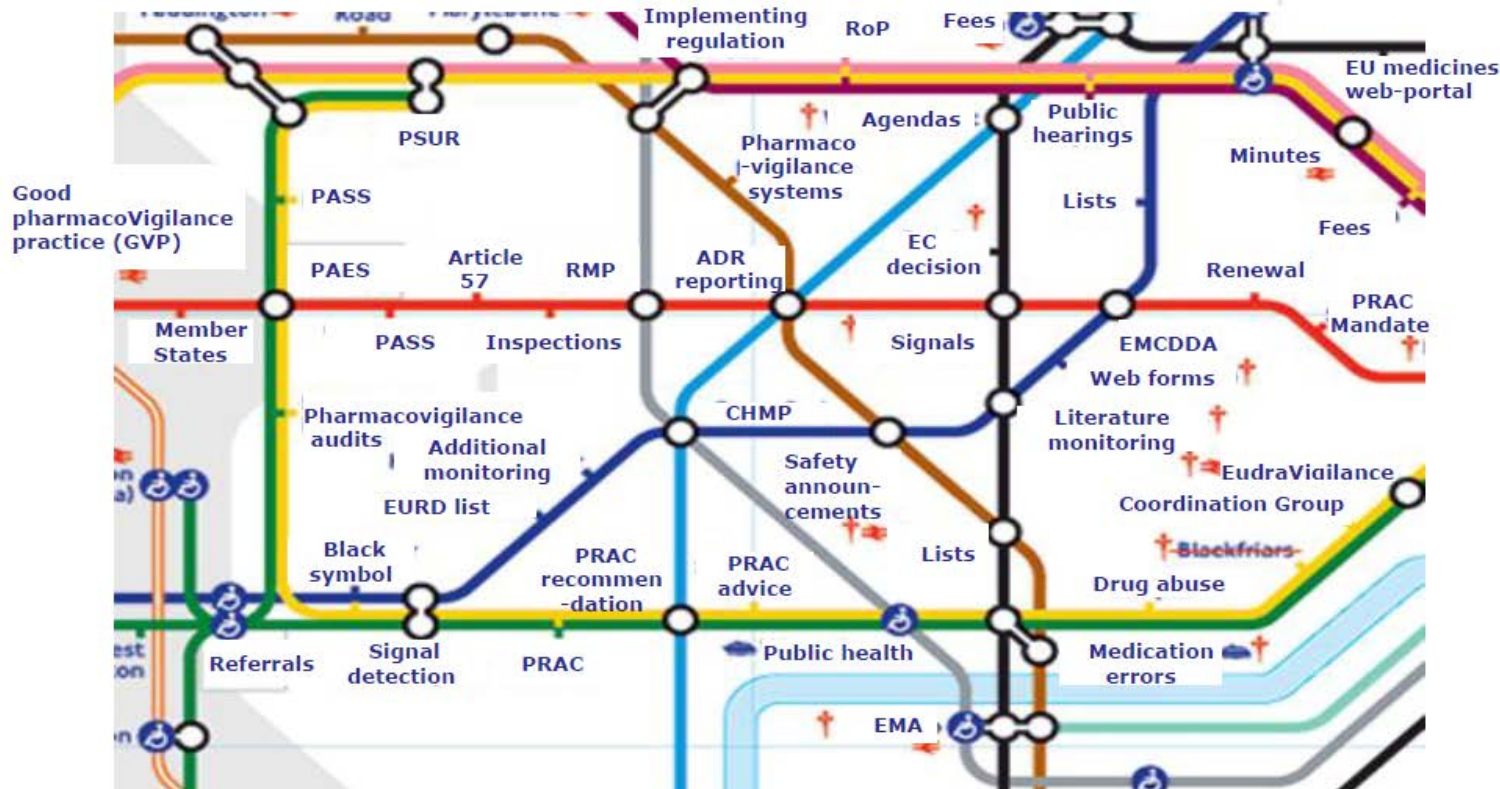
# SCOPE to support MS.....



to find solutions for organising and running their PV system in the context of new legislation in the EU

## Implementation journey....

PHARMACOVIGILANCE



Source: Franck Diafouka, EMA, PCWP and HCPWG Joint Meeting



# Key WP8 target are PV/clinical multitasking assessors:



- ✓ **Identifying** benefits and risks
- ✓ **Assessing** benefits and risks
- ✓ Interpretation and **recommendation**
- ✓ Processes must be **transparent**, documented and communicated

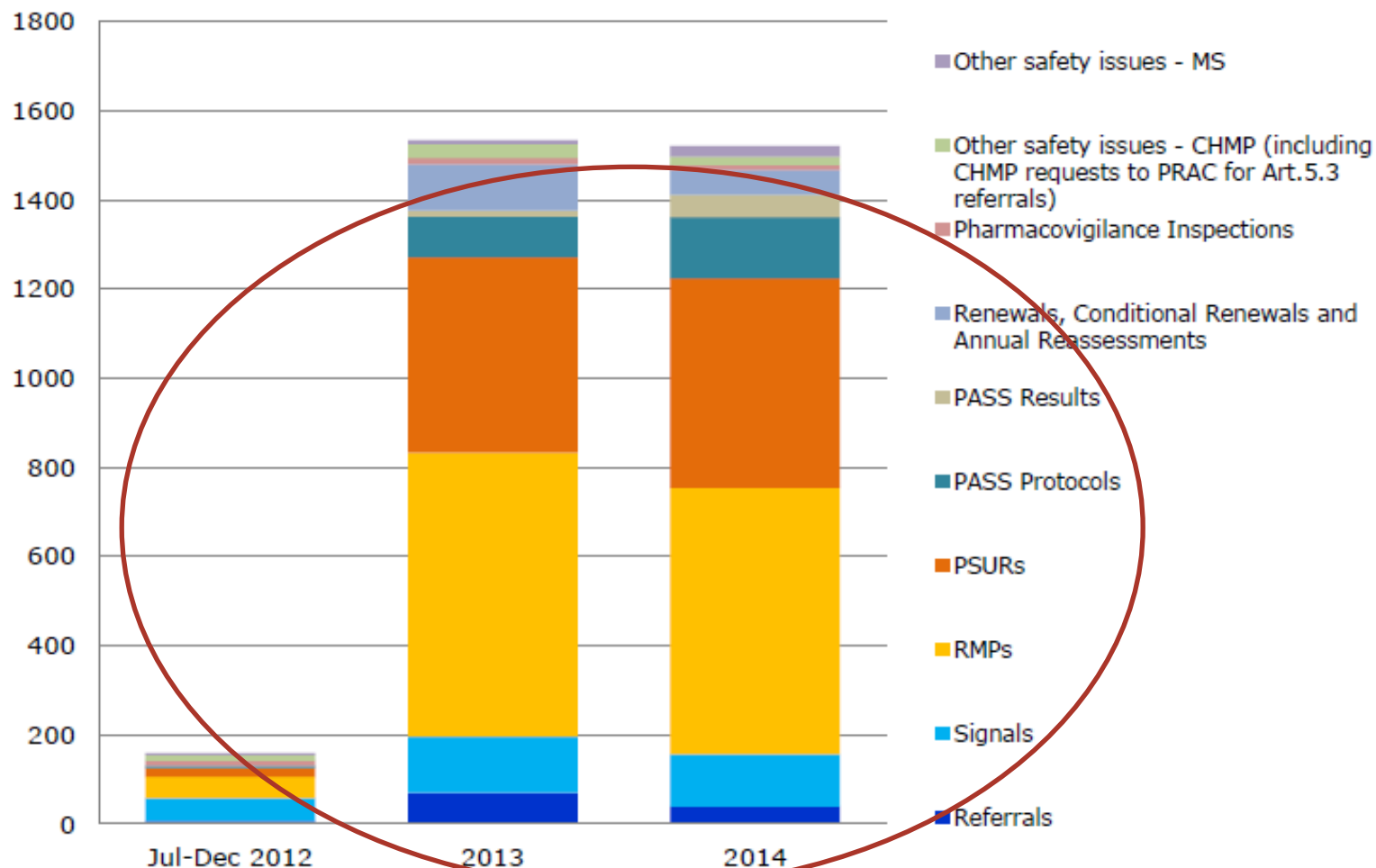
- ✓ a good ability for **integrating data** from multiple sources
- ✓ the estimation of **uncertainty**
- ✓ ability to handle **multiple objectives, differences in perspectives/positions** etc.
- ✓ ability to **work in a team** and to adhere to proposed **timeframes**
- ✓ a good **coordination with other participants and stakeholders** in the process etc

**benefit-risk evaluators often need to learn from prior decisions and experiences**

# Procedures on the PRAC Agenda



Number of items on PRAC agenda



In 2013 we started our work following specific objectives **to promote consistency in PV procedures assessment** throughout the lifecycle:

- ✓To collect **information on existing methods** and processes for PV assessments and deliver a report on good practices useful for NCAs in operating PV effectively and to support the PRAC in its work;
- ✓**To develop a competency framework** in support of PV for human medicinal products throughout the lifecycle: WP8 topics **Recommendations, Practical guides and Training programme;**
- ✓To identify and further elaborate appropriate training materials to assist NCAs to develop/improve their processes and **to maximise training opportunities for PV assessors (e.g e-learning modules).**



# Work Package 8: Lifecycle PV



# SCOPE

Coordination (IT lead) AC: ES, GR, IE, NL, NO,PT, SE, UK

**Topic 1:** IT lead; AC: ES, GR, IE, NL, NO, SE, UK  
**Identification of available data sources outside spontaneous reports**

**Topic 2**

NO lead

AC: ES, IE,IT, SE, PT,UK

**Topic 3**

SE lead

AC: ES,IE,IT,NO, PT,UK

**Topic 4**

IT lead

AC: ES,IE,NO,PT,SE,UK

**Risk  
Management  
Plan  
assessment**

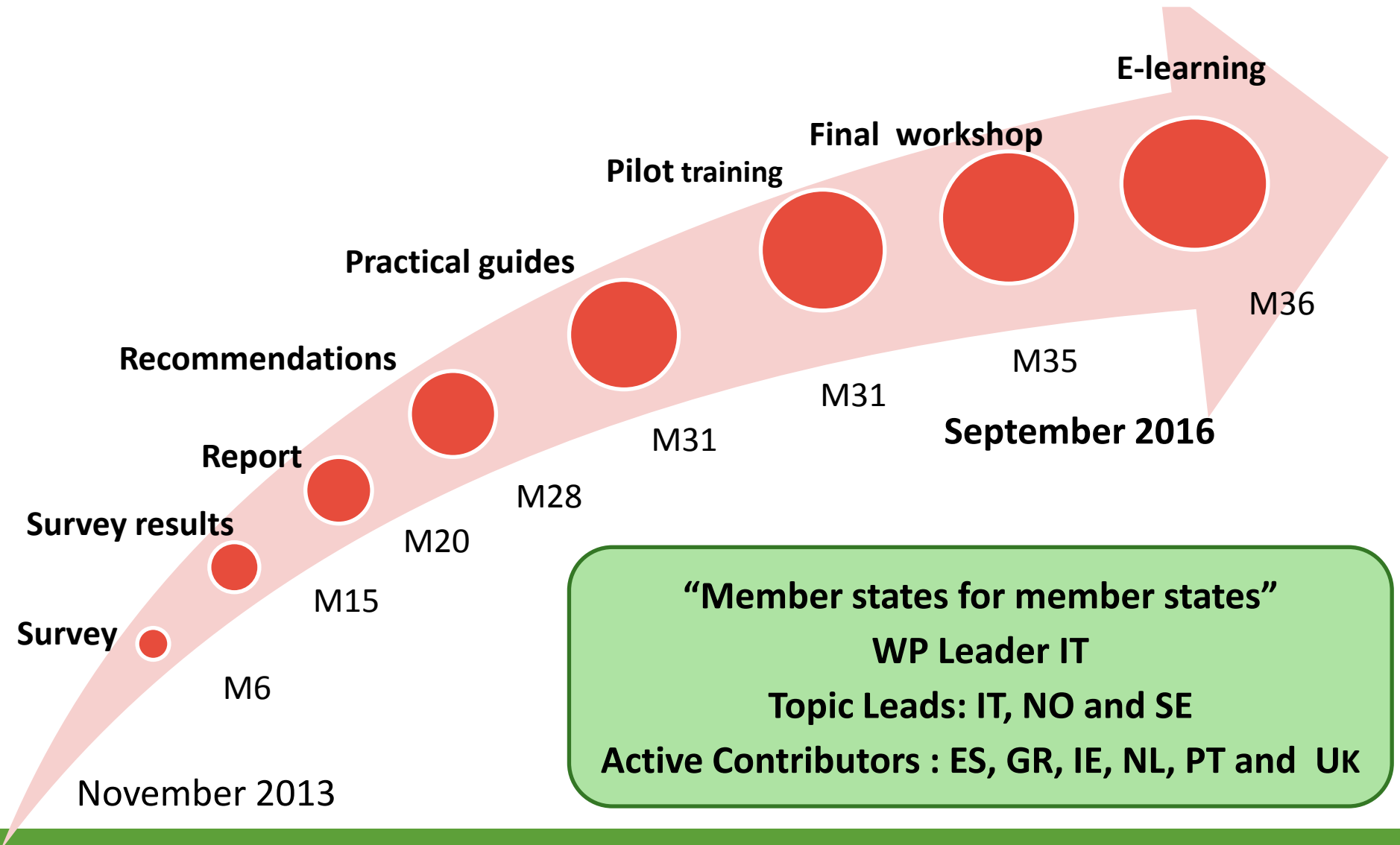
**PASS  
assessment**

**Benefit/risk  
assessment  
PSURs and Referrals**

**Topic 5:** IT lead; AC: ES, IE, UK  
**Competency**

**AC: Active contributors**

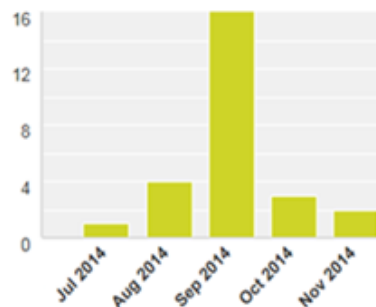
# WP8: Progress and main deliverables



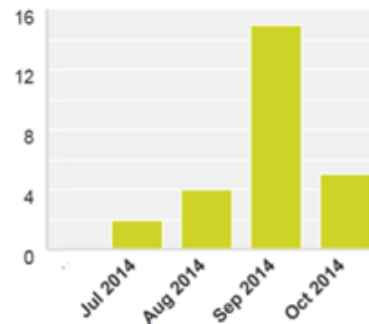
- Conducted from **4th July to 3rd November 2014** and a high response rate of **90% - 25 MS** (3 MS are not official SCOPE partners) was obtained to all five surveys
- All but one of the respondents include RMP, PSUR, referral assessment, evaluation of PASS protocols within their institution's responsibilities

Figure 1. Response rate per month during the surveys:

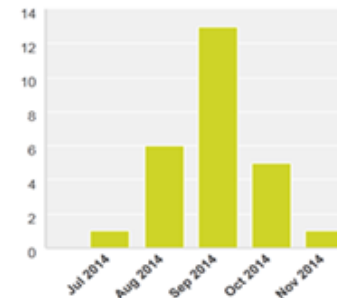
1a) Topic 1-4-5



1b) Topic 2



1a) Topic 3



# WP8: Key survey findings

## Topic 2 - RMPs

The current practice of assessment of RMPs - focus on challenges, possible solutions and good assessment practices.

- **Collaboration** as key element - pre-clinical/clinical/PV assessors
  - ✓ 87% have this possibility

- **Quality of assessment**

- ✓ 60% peer reviewers within agency
- ✓ 45% internal meetings
- ✓ 35% checklists



**Focus in the  
practical  
guidance**

- A “**key challenges**” - areas where more guidance is needed
  - 🤔 **Safety spec** - differentiation between **important/not important** and **identified/potential** safety concerns
  - 🤔 **PhV Plan** - the need for additional studies and design of studies
  - 🤔 **Risk Min Plan** - the need for additional risk minimization and best suitable measures - RMPs for **generic products** – consistency

# WP8: Key survey findings

## Topic 3 - PASS



- 21/25 (**84%**) reported **having had experience in evaluating PASS protocols**
- **20/21 use GVP module VIII as a guideline - half (11/21) use EnCEPP checklist**
- **Joint assessment** considered to be important
- PV assessors , clinical and pharmaco-epidemiology assessors are mainly involved
- 19/24 consider **a general epidemiology support function should be available**
- The mainstay in training is **senior PV assessors acting as mentors**
- Only a limited number of NCAs mentioned some **form of regular training** program for assessors in this field

# Challenging factors in the assessment

	<b>Response Percent</b>	<b>Response Count</b>
<b>Adherence to obligation</b>	30%	6
<b>Assessment of data sources</b>	40%	8
<b>More complex study designs</b>	75%	15
<b>Sample size estimates</b>	35%	7
<b>Analytical strategies</b>	40%	8
<b>Overall feasibility</b>	65%	13
<b>Promotional aspects</b>	50%	10
<b>Quality assurance procedures</b>	10%	2
<b>Total responses</b>		20



# WP8: Key survey findings

## Topic 4 – PSURs and referrals

- Practices for the B/R evaluation – the specific tools**

**Table 1. Specific tools or methods in use facilitating the B/R decision and assessment process**

Answer Options	Response (%)	Response n.
Follow templates/ please describe	87	7
Checklists, please describe	62	5
Decision algorithms, please describe	37	3
EMA Effects Table, please describe	37	3
Tables, please describe	37	3
Mathematical models, please describe	25	2
Other, please describe	12	1
<i>answered question</i>		8
<i>skipped question</i>		17

# WP8: Key survey findings

## Topic 4 – PSURs

- 10 out of 24 NCAs **had experience with procedure** (54 % have an internal SOP) **before** the closure of the survey (**November 2014**) and identified challenges and solutions for the assessment of PSUSAs:

- PSUSA – Lots of PSURs
- Discussion of signal in a generic PSUR only
- Complex procedures and require time for assessment depending on numbers of PSURs and the data there in
- Issues associated with advent of PSUSA procedures e.g. late submissions, lack of awareness of process



# WP8: Key survey findings

## Topic 4 –referrals

### Questions:

1. Use of **external** guidance/templates
  - 50% use guidance
2. Use of **internal** guidance
  - 74% have no SOP but limited experience to date
3. Use and benefits of planning meetings
  - 70% consider to be useful tools
4. Approach to assessment of MAH responses
5. Assessment report review



➤ Complexity of referrals and limited experience supports development of additional guidance

# Main challenges identified

- ✓ Unfocussed/extensive list of questions
- ✓ Challenging timelines
- ✓ Late MAH submissions
- ✓ Unsatisfactory MAH responses
- ✓ Large quantity of complex data
- ✓ SmPCs comparison
- ✓ Medical practice/healthcare infrastructure
- ✓ Clinical context
- ✓ Alternative therapeutic options



**‘Practical  
Guide’**

# Deliverables – ADSs and Competency



## ADSs

**Report**

**List of ADSs detected in the survey**

**Examples of good practices**

**Training session – e.g use of HCR, vaccine and pregnancy exposures**

## Competency

**Report**

**List of available training courses**

**List of useful literature**

**CP and pilot on exchange programme for PV assessors**

**Training session – e.g self-quality assessment check list**

# Recommendations ADSs



- The identification of ADS solely is not sufficient to ensure applicability of ADSs in routine PV practices
- Better definition of ADSs applicability for PV purposes (ADS validation for use in PV procedures assessment)



NEED TO BETTER ADDRESS CHALLENGES RELATED TO ACCESS TO ADSs

- A specific examples from ES, IT and UK of the useful experience with additional data sources have been received in the survey describing consolidated practice with ADSs (included in the Topic 1 Recommendations document – as a part or training material package).



NEED TO INCREASE AWARENESS IN THIS AREA

Specific presentations included in the training course (HC databases, ADSs for evaluation of vaccine and pregnancy exposure safety issues)

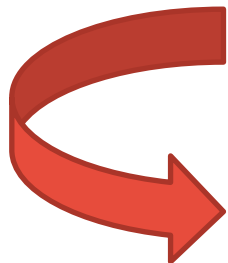


# Training materials and other useful tools for PV assessors



**Competence** is the ability of an individual to do job successfully and efficiently

- Implementation of **quality system** (e.g. SOPs, mentoring system, introduction programme, obligatory trainings) for newly employed assessors and for maintenance of assessors' knowledge.
- Implementation of **continuing professional development programmes**, personal educational forms (a format that allows recording of attended trainings) for the motivation of assessors' participation in training events.



**THE EXCHANGE PROGRAM FOR ASSESSORS - Proof of concept - grounds for a sustainable exchange programme for European PV assessors**

# Deliverables – RMP, PASS, PSUR and referral topics



# SCOPE



Training course



SCOPE Work Package 8 -  
LIFECYCLE  
PHARMACOVIGILANCE  
Executive Summary Report

E-learning  
modules

**WP8  
Training  
package –  
14  
deliverables**

Reports

SCOPE Work Package 8  
Lifecycle Pharmacovigilance

Practical Guide  
on PSUR / PSUSA  
Assessment

2018



Practical guides

SCOPE Work Package 8  
Lifecycle Pharmacovigilance

PASS  
Recommendations

2018



Recommendations

## WP8 Practical guidance **in addition to formal regulatory documents** and national SOPs

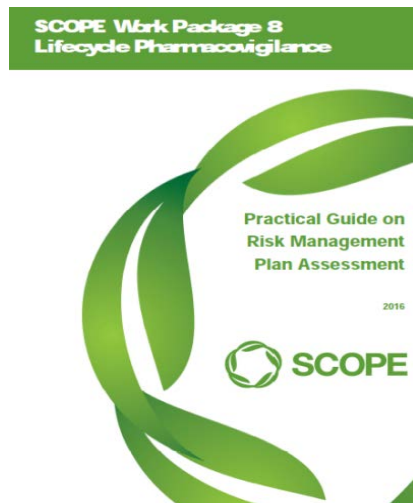
- Not to replace existing guidance (GVPs)
- Not intended to advise on procedural aspects or to influence templates and guiding text provided by EMA



## The guidance **are based on**

- Responses to a **WP8 survey** in 2014 to NCAs on current practices, challenges and solutions
- **Practical experiences** in European procedures

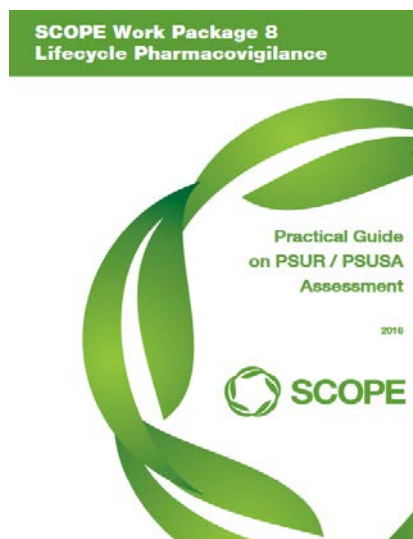
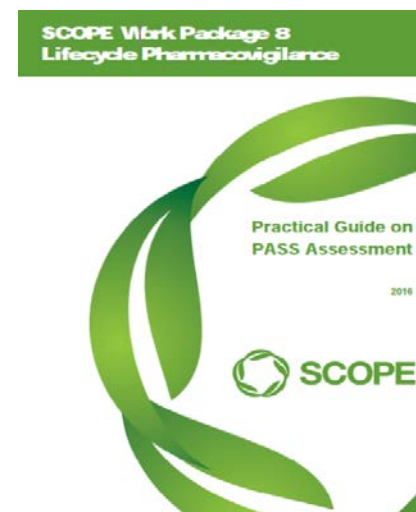




➤ Key challenges and learnings from PRAC on handling PV procedures assessment

➤ Practical advice on some aspects

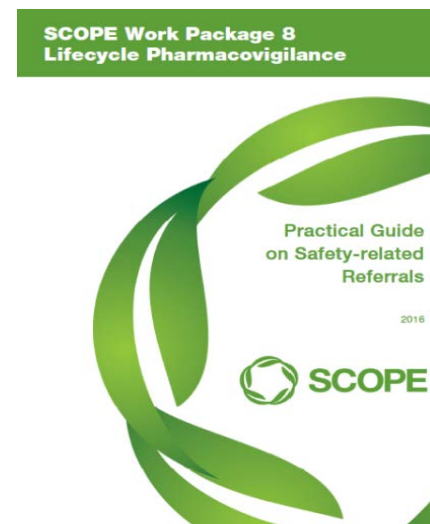
➤ “From assessors for assessors”



- Planning time and resources
- Getting the scope right
- Value of Expert Advice
- Delivering the consistent assessment report/package

Specific for referral:

- Oral explanations
- Public hearings



# Deliverables: Training course



# SCOPE

**to share experience  
and practical advice**

**Opportunity for  
exchange of ideas**

**to increase the  
awareness on  
some specific  
aspects of PV**

**to discover new  
tools** that could  
facilitate the  
assessment of PV  
procedures



**to learn more  
from each other  
and to increase  
consistency in our  
work**

**123 participants  
From 26 MS and  
3 from EMA  
20 speakers from 9 MS**



# SCOPE

**Work Package 8  
Lifecycle Pharmacovigilance  
Final Training  
Lisbon, 20 and 21 September 2016**

**50 % reply rate to  
the evaluation  
questionnaire  
18 MS**

# Deliverables: e-learning modules

- RMP
- PASS
- PSUR/PSUSA
- referral




**.....to maximise training opportunities for PV assessors**





00\_02

 SCOPE

**Introduction** ✓

**What is a safety referral procedure?**

**Key stages in a referral**





**Other considerations**

**When you're not (co)-rapporteur**


**Summary** ✓


**Quiz**


This course contains seven sections. Select each heading to go to that section.


   

1/52 >


 **Menu:**  
Select here to return to the main menu for this e-learning

 **Resources:**  
Select here to access your bank of resources for this e-learning

 **Help:**  
Select here for help on how to use the screens


 **Exit button:**  
Select here to exit the course at any time

1/52

 **Forward and back arrows:**  
Use these arrows to navigate backwards and forwards through the course

[https://www.walkgroveonline.com/MHRA/WP8/wp8sr\\_gold\\_2/story.html](https://www.walkgroveonline.com/MHRA/WP8/wp8sr_gold_2/story.html)

03\_01





 SCOPE

**Key stages in the referral procedure**

**Key stages and other important considerations**


This interactive timeline illustrates key stages and other important considerations during a referral from an assessor's perspective. Click on the stages to jump to the relevant section.

Select each of the **stages** to find out more.

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07\_01

 SCOPE

**Quiz**

**Question 1:**  
**The purpose of a safety referral**

What is the purpose of a safety referral (article 20, article 107i, article 31)?





That's still not quite right, the correct answers are highlighted.

A more appropriate way of harmonising the SmPC and PIL between nationally-authorised products in all member states would through an article 30 referral procedure.

Requesting additional data is a possible outcome of a referral but is not generally the reason for triggering one.

Resolving differences of opinion between MS raised during a safety variation assessment should be done via an article 13 referral arbitration procedure. article 13 referral arbitration procedure.

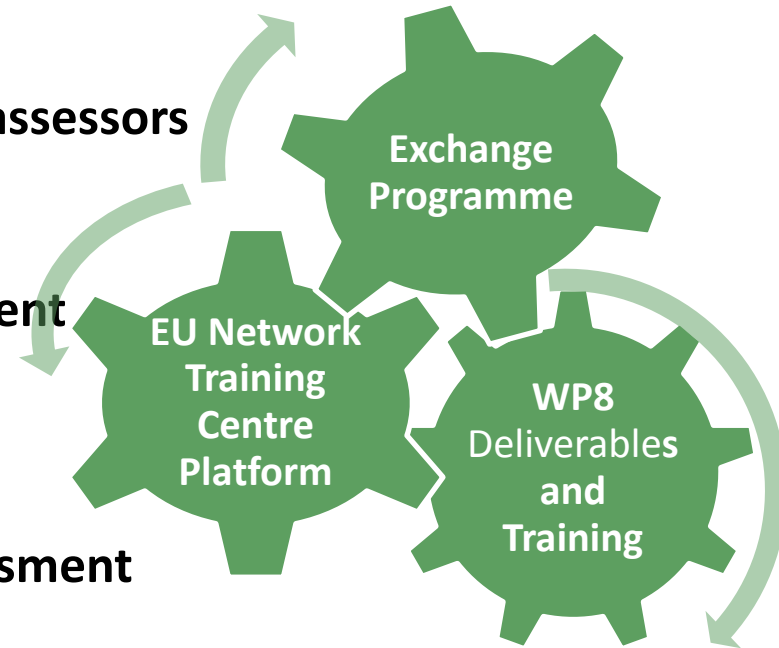
- To harmonise the SmPC and PIL between nationally-authorised products in all member states
- To establish if additional data would be useful to support the positive B/R balance of the product
- To resolve issues over the safety or balance of benefits and risks of a medicine or class of medicines
- To establish whether measures to minimise harm to patients are required throughout Europe
- To resolve differences in opinion between MS raised during a safety variation assessment
- To establish whether the MA for a product or group of products should to be varied, maintained, suspended or revoked in the light of concerns about safety or the balance of benefits and risks

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# Benefits for EU PV network

- ✓ **Contribution to EU Pharmacovigilance Training Curriculum**
- ✓ **Maximizing of training opportunities for PV assessors (e.g e-learning moduls)**
- ✓ **Identification of areas where more commitment is needed (e.g use of ADSs and evaluation of effectiveness of RMMs)**
- ✓ **Promotion of consistent PV procedures assessment**
- ✓ **Evaluation of the quality of assessment – provided by WP7 and presented also in WP8 training**
- ✓ **Promotion of collaboration among NCAs and MS**





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# Questions?

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Now this is not the end.  
It is not even the beginning of the end.  
But it is, perhaps, the end of  
beginning.  
— Winston Churchill