MHRA
Regulating Medicines and Medical Devices

Good Pharmacovigilance Practice

Overview of GVP Modules on ADR, PSURs, Signal Management and Additional Monitoring

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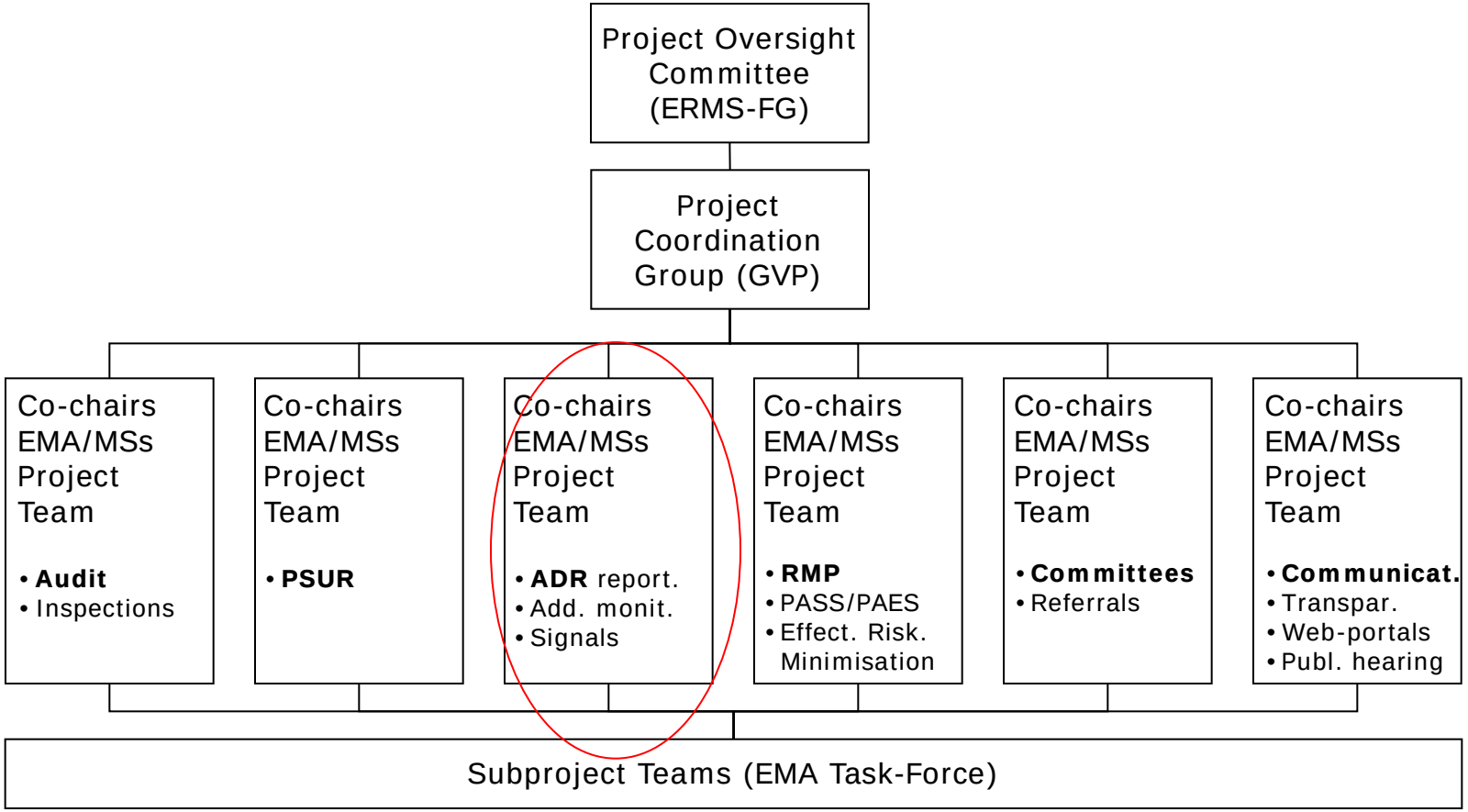
Content

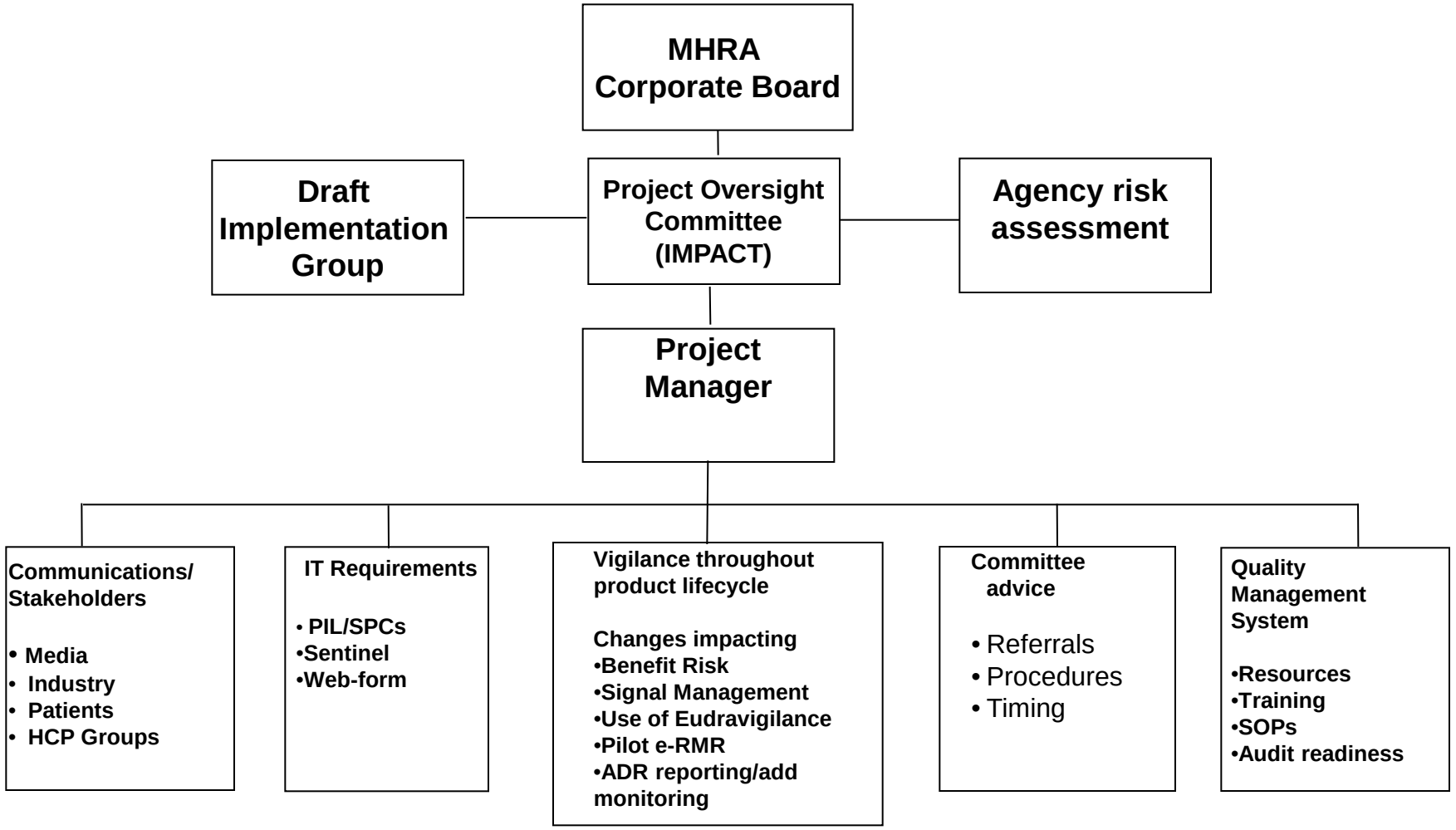
- ADR Reporting
  - Definition & Increased scope
  - Transition arrangements
- Additional Monitoring
  - Process & Timetable
- PSURs
- Signal Management
- EU Joint Action

The Process

Governance of the Implementation of the New Pharmacovigilance Legislation



National Implementation Governance



ADR reporting

Directive 2010/84/EU
Article 1

11. Adverse reaction: A response to a medicinal product which is noxious and unintended

Article 107(3)

MAHs shall submit to Eudravigilance:
all serious ADRs that occur in the Union and in third countries within 15 days……..
All non-serious ADRs that occur in the Union within 90 days……

ADR reporting

Directive 2010/84/EU

(Chapter 5) For the sake of clarity, the definition of the term 'adverse reaction' should be amended to ensure that it covers noxious and unintended effects resulting not only from the authorised use of a medicinal product at normal doses, but also from medication errors and uses outside the terms of the marketing authorisation, including the misuse and abuse of the medicinal product.

Note: Includes error, off-label, study reports

ADR reporting

Medication error

- Often not part of traditional PV system
- Other agencies may have responsibility
- Data sharing agreements will be important
- Signal detection methodologies need to be considered
- Effective communications with healthcare providers should be considered

Excellent workshop held 28th Feb/1st March

- Report and action plan on EMA website

ADR reporting

Off-label/Unlicensed

- As for all other ADRs only where harm has occurred
- To be discussed in the PSUR
- To be included in the company database
- Effective communications with healthcare providers should be considered

ADR reporting

Study Reports

- GVP has caused concern regarding studies such as patient support programmes and non interventional studies
- GVP update is being worked on. To be ready July 2013
- Workshop to be held at EMA to inform development of guidance on PSPs

ADR reporting

Directive 2010/84/EU

Article 2 – Transitional Provisions

- Eudravigilance functionality to be met first
- Functional requirements to be drawn up by MSs and Agency
- Functionalities to be audited
- Article 107(3) applies 6 months after audit

ADR reporting

Marketing authorisation procedure	Origin	Adverse reaction type	Destination	YES	
• Centralised • Mutual recognition, decentralised or subject to referral • Purely national	EU	All serious	Member State where suspected adverse reaction occurred only	AT, CZ, DE, DK, ES, FI, IE, IT, LT, LV, NO, PT, RO, SI, SK, UK	
			Member States where medicinal product is authorised & Eudravigilance	BG, HU	
			Eudravigilance Only	BE, CY, EE, FR, GR, IS, LI, LU, MT, NL, PL, SE	

ADR reporting

Marketing authorisation procedure	Origin	Adverse reaction type	Destination	YES	NO
• Centralised • Mutual recognition, decentralised or subject to referral • Purely national	EU	All non-serious	Member State where suspected adverse reaction occurred	AT, DE[1] DK, IS, PL, RO	BE, BG, CY, CZ, DE, EE, ES, FI, FR, GR, HU, IE, IT, LI, LT, LV, MT, NL, NO, PT, SE, SI, SK, UK
	Non-EU	All serious	Member States where medicinal product is authorised	DE, SK, UK	AT, BE, BG, CY, CZ, DK, EE, ES, FI, FR, GR, HU, IE, IS, IT, LI, LT, LV, MT, NL, NO, PL, PT, RO, SE, SI,

DE[1]: Only for non-serious cases related to vaccines reportable to the Paul-Ehrlich-Institut. Reporting of other non-serious cases related to non-vaccines medicinal products will only be requested individually in case of safety concerns.

LU: Information not provided.

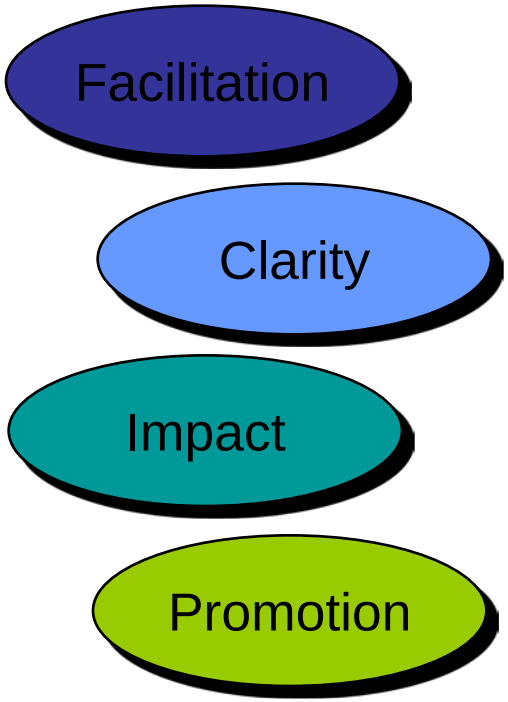
"Directive 2010/84/EU… Article 102. The Member States shall:

….take all appropriate measures to encourage patients, doctors, pharmacists and other health-care professionals to report suspected adverse reactions to the national competent authority; for these tasks, consumer organisations, patients organisations and healthcare professionals organisations may be involved as appropriate."

Need to raise general awareness of legislation

Yellow Card Strategy

- **Raise awareness and understanding of the Yellow Card Scheme**
- **and increase reporting**



Increasing access to the scheme to meet the needs of reporters e.g. integration with clinical systems

What to report and when

How Yellow Card reporting makes a positive difference

Develop and maintain promotion and communication strategies for the scheme

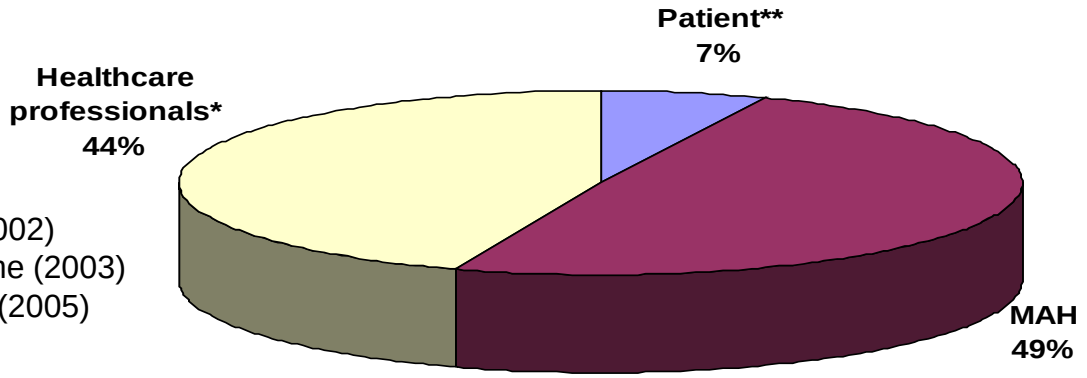
Two complementary sets of activities

(1) healthcare professionals (2) the public

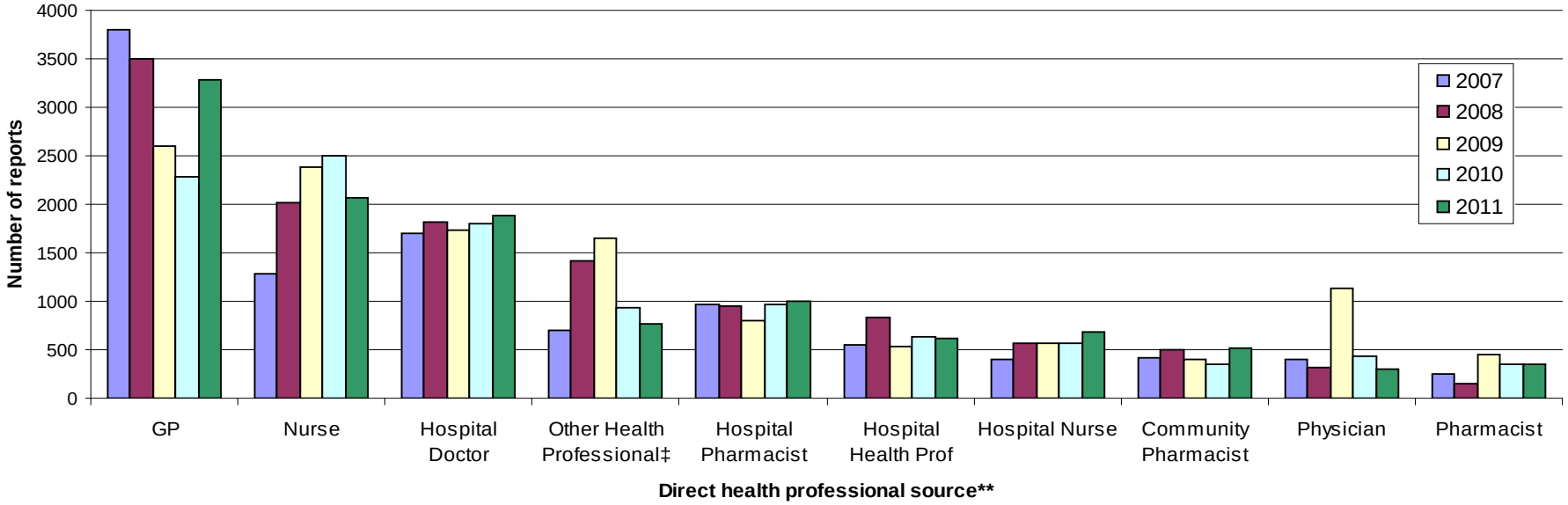
UK spontaneous reports

Extensions to Scheme:

- Coroners (1969)
- Pharmacists (April 1997 & Nov 1999)
- Nurses, midwives and health visitors (2002)
- NHS Direct patient reporting pilot scheme (2003)
- Patient reporting pilot scheme UK-wide (2005)
- Patient reporting established – Feb 08



Sources of direct health professional reports 2007 - 2011



Electronic reporting

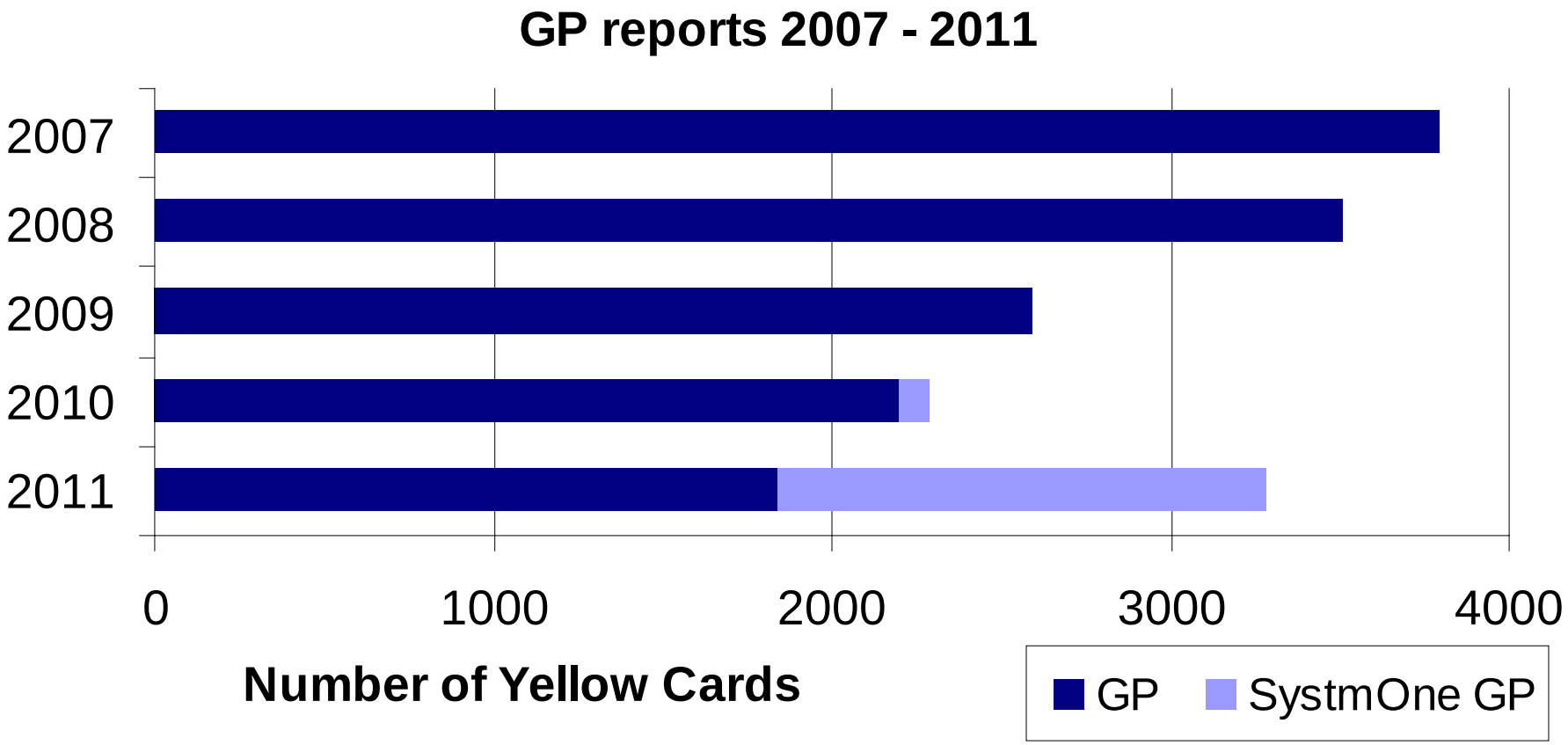
– SystmOne (GP system) (15-20% England GP practices)
  - Reported >2,500 since November 10
  - Over 1700 received in one year
  - ~50% increase in GP reporting

– Pilot ongoing with Cerner - Newcastle NHS Trust

– NHS information Standard – ISB 1582 electronic Yellow Card reporting
  - GP Systems of Choice

- UKMI Centres went live in 2010

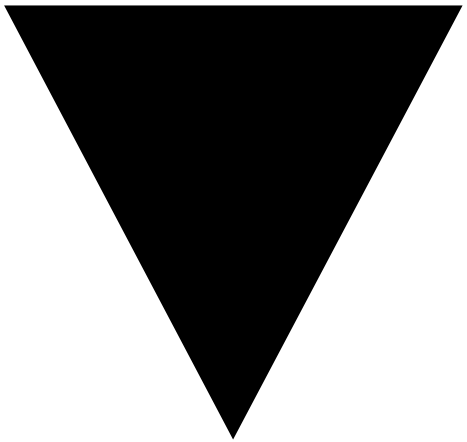
Electronic reporting



‘EU-wide monitoring’

“Directive 2010/84/EU…

(10)…some medicinal products are authorised subject to ***additional monitoring****. This includes all medicinal products with a* ***new active substance and biological medicinal products, including biosimilars, which are priorities*** *for pharmacovigilance.”*

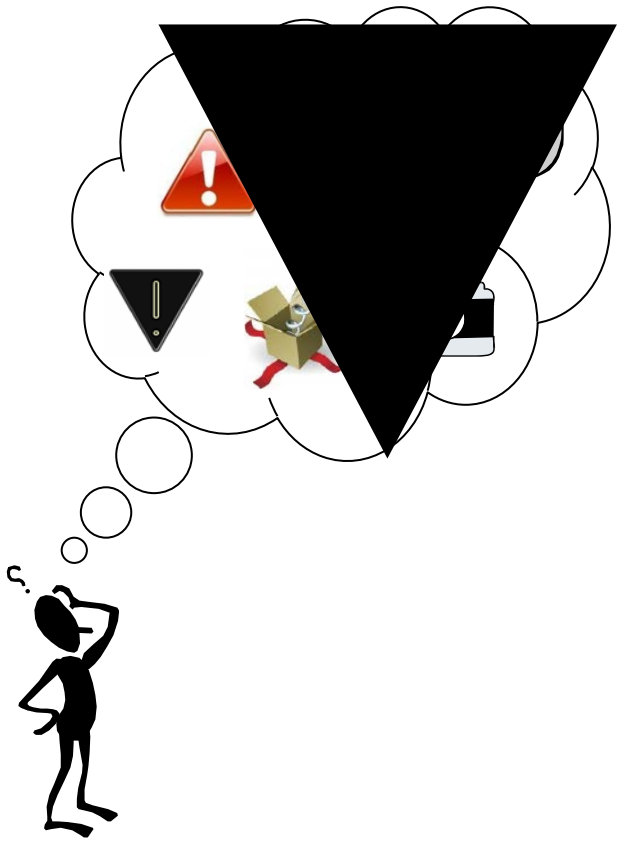


Additional Monitoring GVP Module X

- Similar to UK Black Triangle Scheme
- List to be maintained by EMA and include:
  - all new active substances – *mandatory scope*
  - any biological product – *mandatory scope*
  - others subject to consultation with PRAC – *optional scope*
- Removal from list reviewed at 5years – can be extended subject to PRAC agreement
- Black symbol – exact details agreed by EC following PRAC recommendation
- QRD Group have considered and consulted with patient & HCP groups

Selecting the black symbol

- **Alternative symbols** provided by Member States, which may be developed as the black symbol:
  - Magnifying glass
  - Eye
  - Exclamation mark
    - ✓Within a box
  - Camera
  - Black triangle
    - ✓With a magnifying glass inside
    - ✓With an exclamation mark inside



List Published

- Mandatory Scope list published 25th April
- Type 1A variation to update PIL & SmPC required by 31 December 2013
- All new MAs from 1 September to comply with QRD template
- Optional Scope list to be published after PRAC consideration

Periodic Safety Update Reports (PSURs) – Module VII

Key changes

- Single PSUR assessment for products authorised in more than one member state
- EURD list
- Obligation on MAH to submit evaluation of risk-benefit balance
- Reduced requirements for submission of PSURs for generics, well established use etc
- Establishment of a PSUR repository - awaited

Key documents

- Guideline on good pharmacovigilance practices (GVP)

  Module VII-Periodic safety update report

  Covers: Structures and Processes
  Guidance On New format
  Operation of the EU network

- ICH E2C(R2)

- EMA Q&As (updated November 2012)

New focus

- No routine requirement for line listings- but can be requested
- New focus on summary information, scientific assessment and integrated risk-benefit evaluation
- Waiver for generics, well-established use, homeopathic and traditional herbals
- Assessment focused on determining whether there are new risks or whether risks have changed or whether there are changes to the risk-benefit balance of medicinal products

Frequency

- **For products authorised before July 2012**
  - Every 6 months during the first 2 years following the initial placing on the market, once a year for the following 2 years and at three-yearly intervals thereafter.

- **According to a condition of the Marketing Authorisation**

- **According to the List of European Union Reference Dates (EURD)**

- **PSURs also need to be submitted upon request from a Competent Authority**

What has improved?

- Strengthened focus on evaluation of available information from multiple data sources
- Overview of safety signals and safety evaluation
- Overview of benefits and benefit evaluation
- Strengthened link with risk management planning
- Modular structure addresses duplication with RMP
- Stand alone report based on cumulative data- facilitates assessment process
- Supports lifecycle approach to continuous benefit-risk evaluation

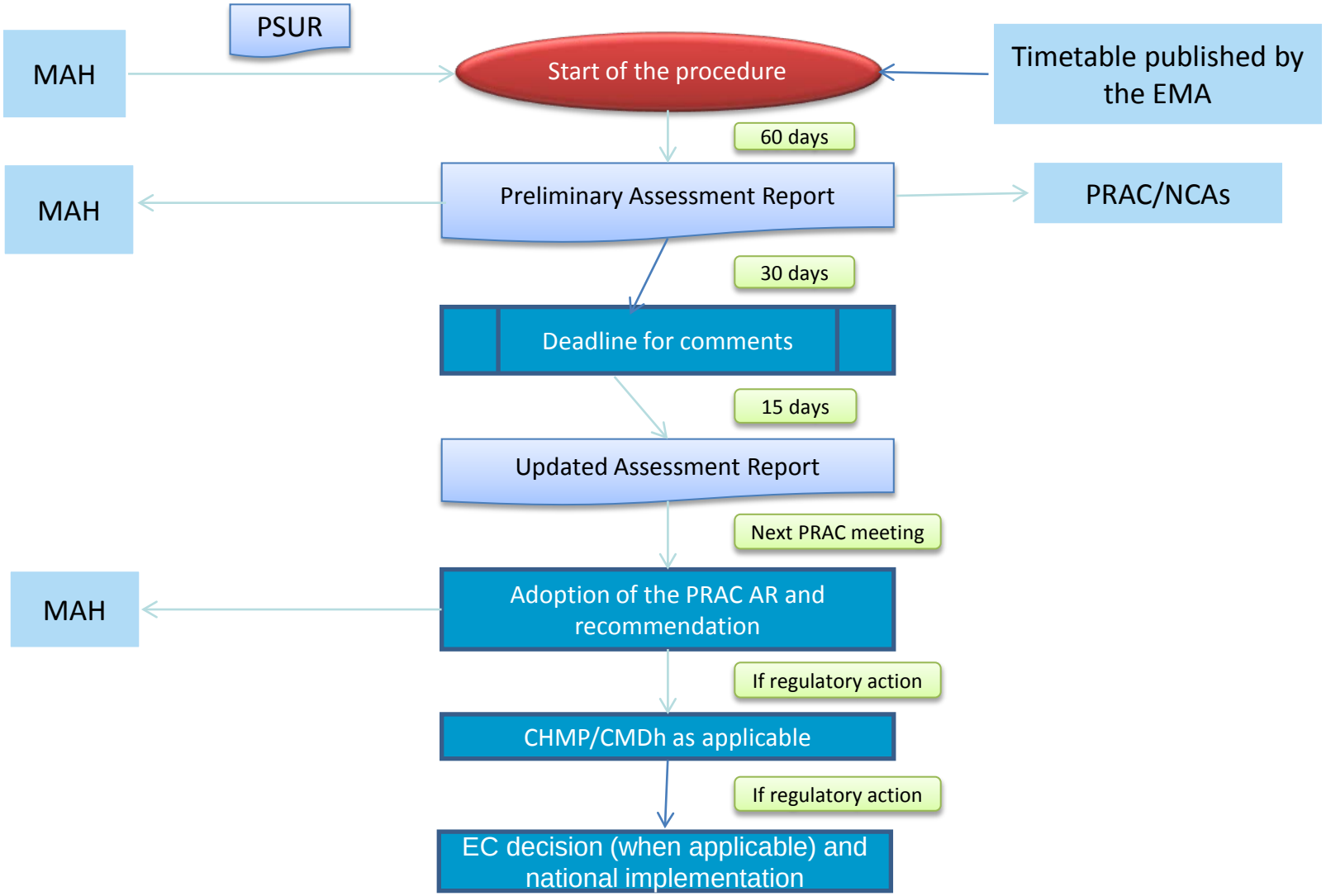
To note

- Risk evaluation should be based on all use of the medicinal product including evaluation of safety in real medical practice, use in unauthorised indications and use which is not in line with the product information

- Critical gaps in knowledge with use of the product for specific safety issues or populations, (e.g. use in paediatric population or in pregnant women) should be reported in the PSUR

- Efficacy and effectiveness – the scope of the benefit information should include both clinical trial and real life data in authorised indications

Single Assessment



Signal management - GVP Module IX

- Largely follows CIOMS VIII guidance:

- Detection – most appropriate method:
  - Review of ICSRs
  - Statistical Analysis
  - Combination of the two
- Validation
- Prioritisation
- Evaluation
- Action
- Information exchange

Action based upon a signal

- Actions should be carried out at the most appropriate step in the process (workflow is flexible)

- When activities are requested by a CA they should specify timeframes including:
  - Completion
  - Progress reports and interim reports
  - Should be proportionate to severity & public health impact

- CAs and MAHs should consider feasibility when proposing the above

Exchange of information (1)

- CAs, MAHs & Others may need to exchange information on signals:
  - Timing is dependent on the safety issue, but information on signals should (in general) only be communicated if the signal has been validated
- CAs should communicate results of signal evaluations to MAHs

Exchange of information (2)

- MAHs should communicate any relevant information regarding safety signals to competent authorities as part of their pharmacovigilance obligations and on-going monitoring of the benefit-risk of the medicinal products.

- Validated signals that may have implications for public health and the benefit-risk profile of the product in treated patients should be **immediately** communicated to the competent authorities.

Quality requirements

- **Tracking**: evaluations, timelines, reporting and any key steps must be recorded and tracked systematically (for both validated & non-validated signals

- **Quality systems & documentation:** Quality control consistent with ISO 9001 standards should be applied to all signal management processes. Full audit trail should be available

- Training: All staff that may identify a signal should be trained in signal processes (not just PhV teams)

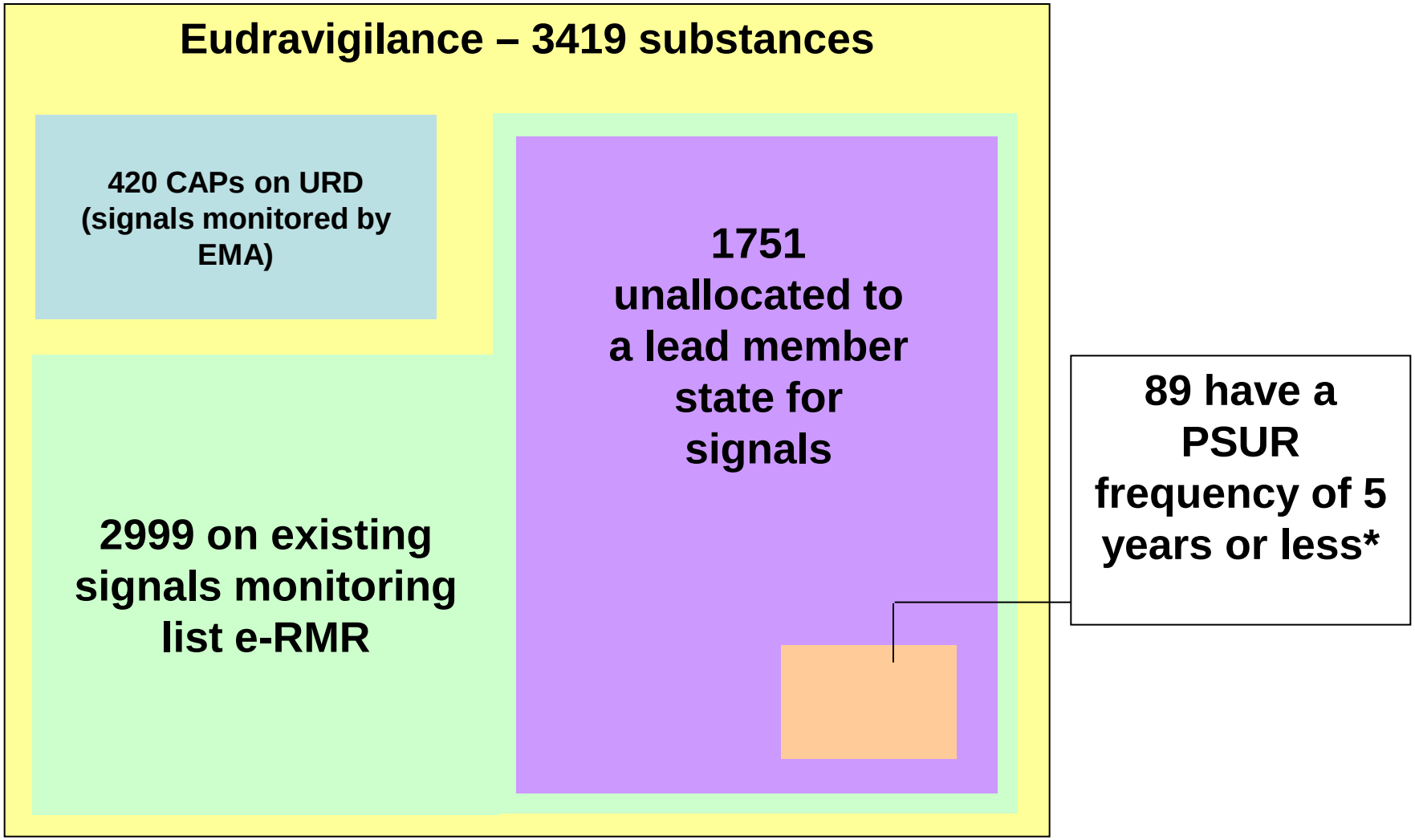
Roles & Responsibilities

- Most roles have shared responsibilities in the EU regulatory network:
- Monitoring of Eudravigilance for signals: EMA, NCAs (MAH)
- Signal management: EMA, NCAs, PRAC, MAH
  - Lead Member states assigned via EU RD list

The MAH

- Shall monitor the data to the extend of their accessibility to the EV database
- Shall monitor all emerging data and perform signal detection activities including the validation of signals
- Shall communicate any validated signals according to an internal procedure to the EMA or NCAs, for further validation
- Should collaborate with the PRAC for the evaluation of the signals by providing additional information upon request
- Shall keep an audit trial of their signal detection activities

Signal Detection lead



EU Joint Action Project

Objectives

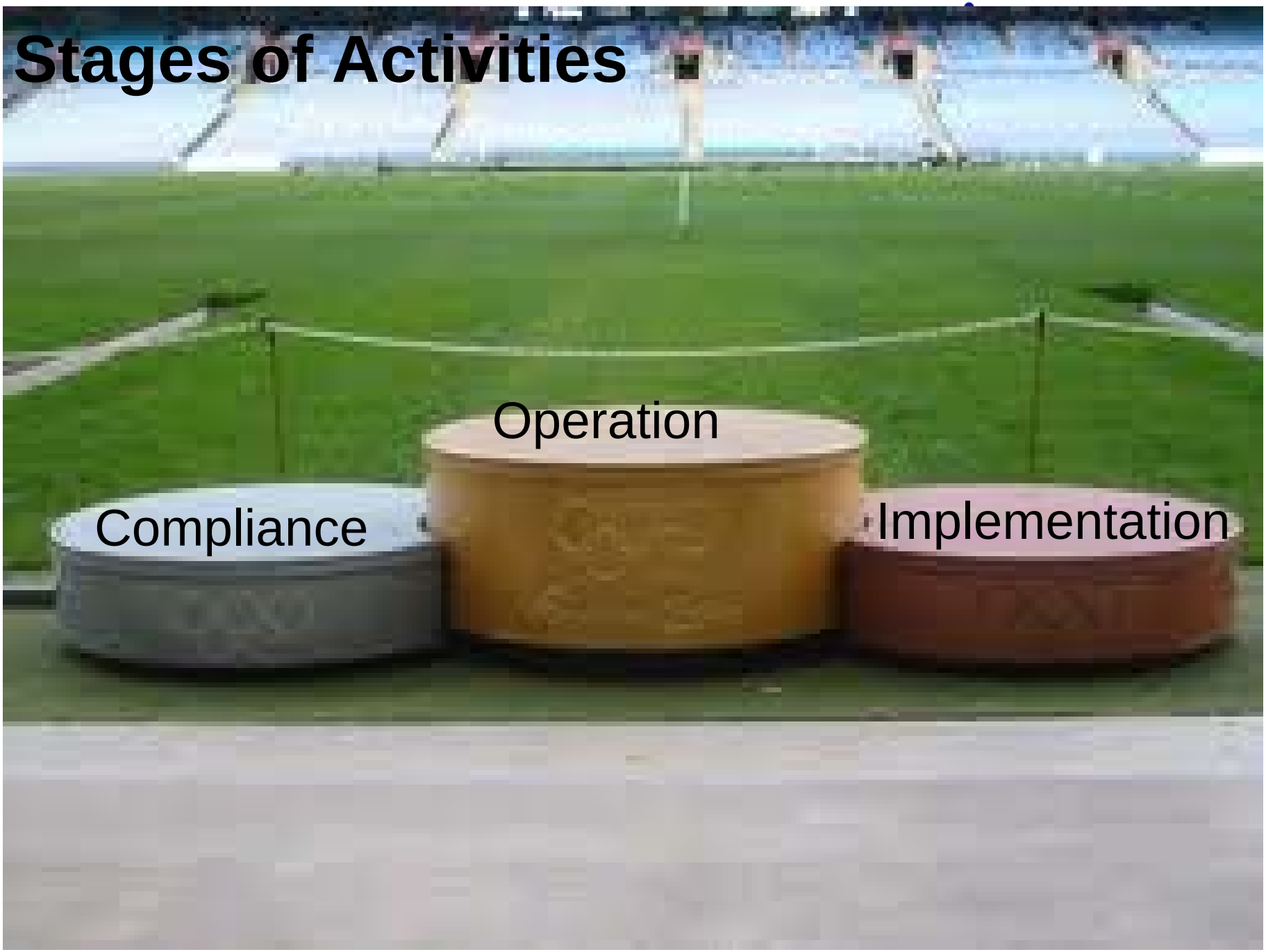
Under "Improve citizens' health security" objective

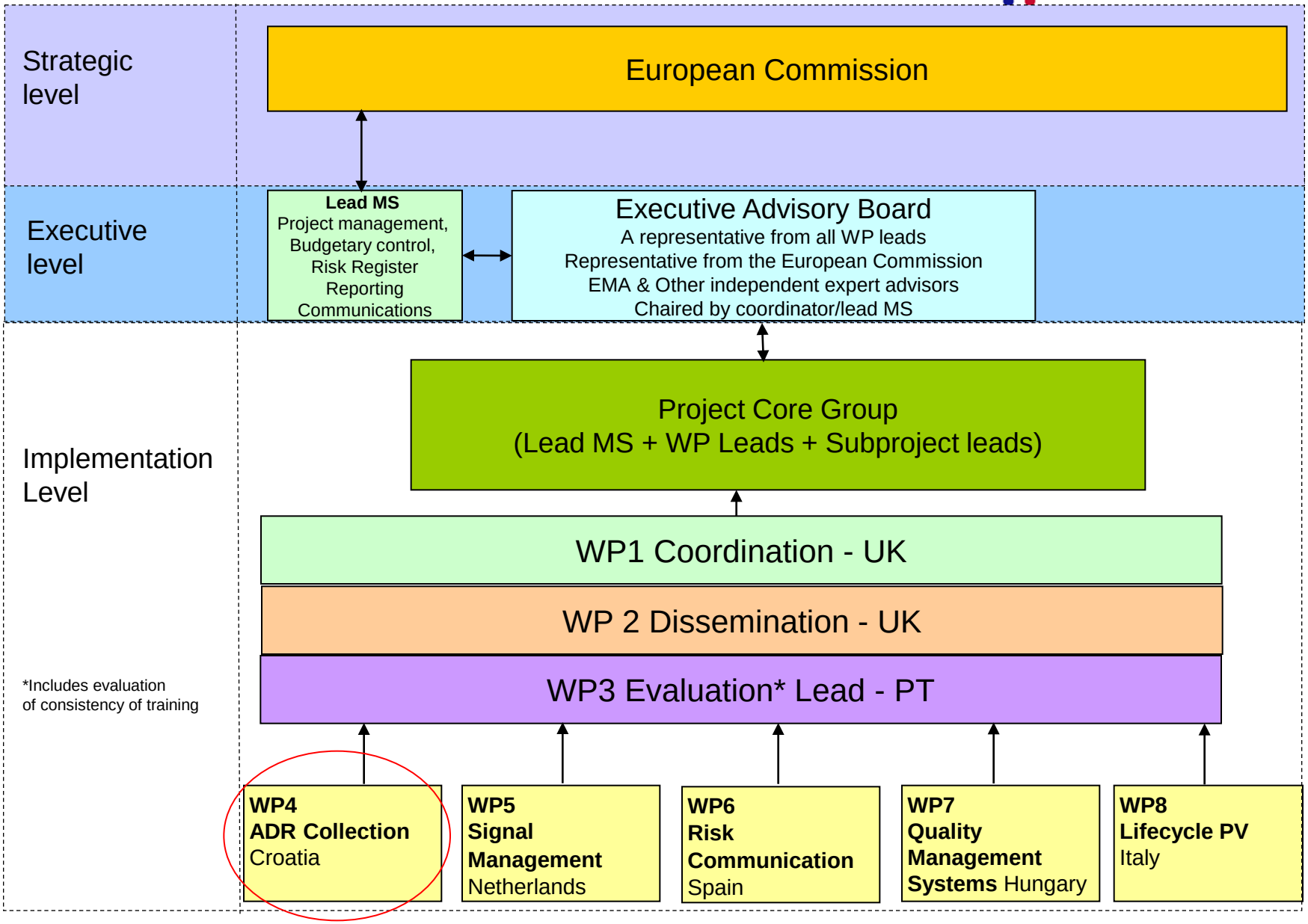
Facilitating collaboration among the Member States for the effective operation of the pharmacovigilance system in the EU

Support Member States to find solutions for organising and running their pharmacovigilance system in the context of the new pharmacovigilance legislation in the EU

Exceptional utility co-financing - 70% EU funding

Stages of Activities




Strategic level
European Commission
Executive level
Lead MS
Project management,
Budgetary control,
Risk Register
Reporting
Communications
Executive Advisory Board
A representative from all WP leads
Representative from the European Commission
EMA & Other independent expert advisors
Chaired by coordinator/lead MS
Implementation Level
Project Core Group
(Lead MS + WP Leads + Subproject leads)
WP1 Coordination - UK
WP 2 Dissemination - UK
WP3 Evaluation* Lead - PT
*Includes evaluation of consistency of training
WP4 ADR Collection Croatia
WP5 Signal Management Netherlands
WP6 Risk Communication Spain
WP7 Quality Management Systems Hungary
WP8 Lifecycle PV Italy

- Health Programme 2013 adopted 2nd Oct 2012
- Expression of interest 25th Oct 2012
- Workshop in Luxembourg 10/11 Dec 2012
- Application form released 20th Dec 2012
- QA workshop in Luxembourg 18/19 Feb 2012
- Deadline for submission 21st March 2013
- Contract negotiations July 2013
- Project commencement from Sept 2013

Summary

- After a long time in the making the new system is alive
- Member States have had to engage as fully as industry
  - We have tried to support MAHs
  - Development of GVP
  - Lots of internal training and revision of internal standard operating procedures
- Still a number of outstanding issues and transition
- Further initiatives to come to help member states operate the new system to the highest possible standards

Questions