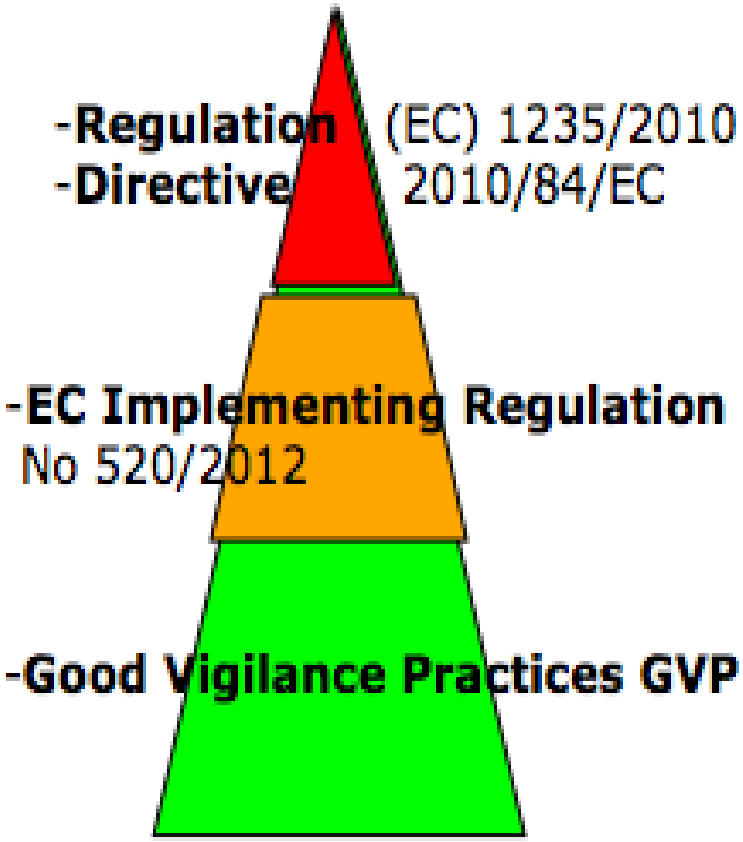
SCOPE Work Package 5
Signal Management

From implementation to operation

London
23 November 2016

For Signal Management

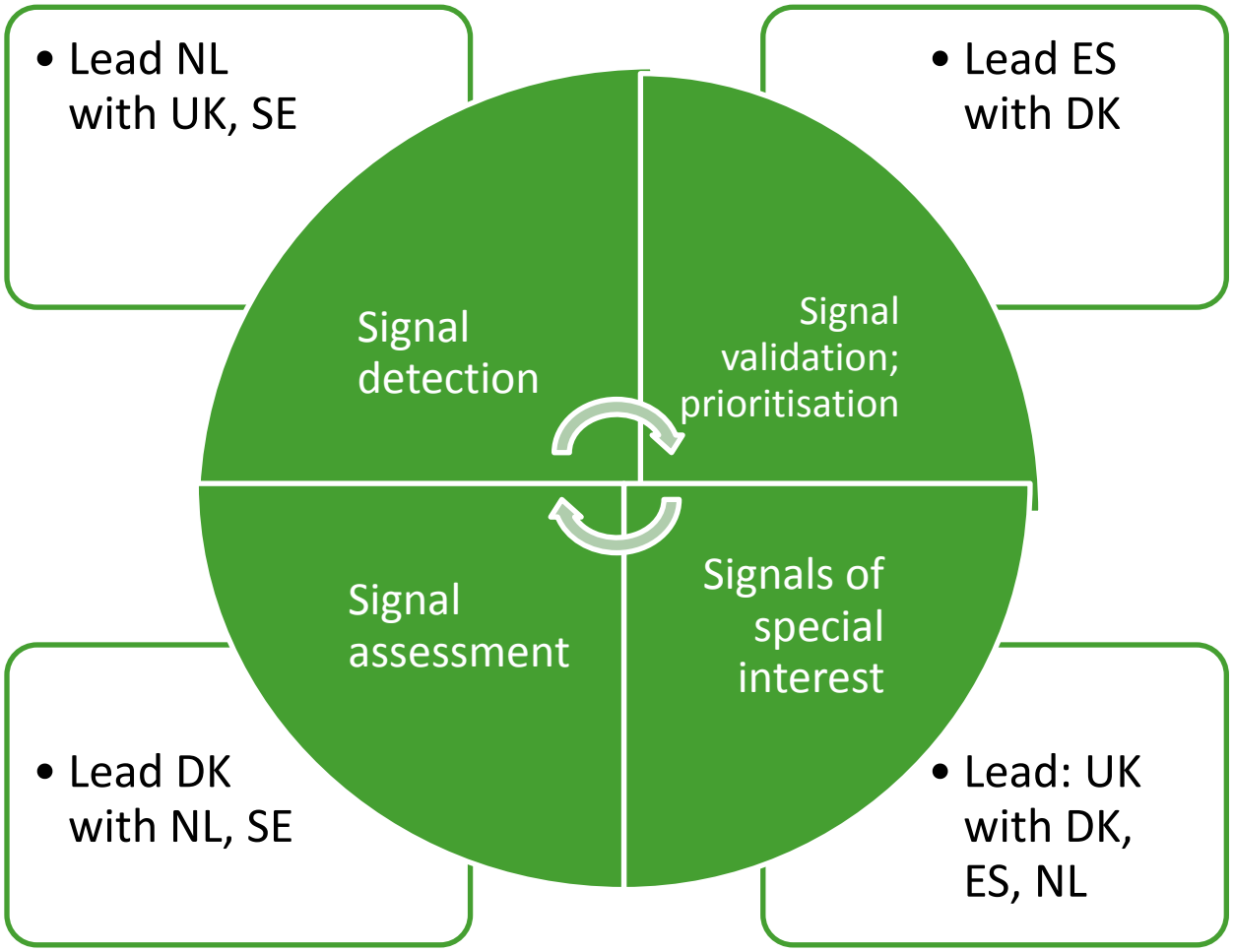
- ✓ Implementing regulation
- ✓ CIOMS Working group VIII
- ✓ GVP IX
- ✓ EMA Q&A
- ✓ SCOPE WP5: Best Practice Guidance (BPG)
  E-learning



Work Package 5 – Signal Management

- WP 5 – Best practice in signal management within the network of National Competent Authorities (NCAs)

> *'create and deliver recommendations for **consistent** and **timely** procedures for the timely management of safety signals across the EU network. (…)'.*
>
> *'(…) Additional focus on detection and management of **signals of special interest**, such as those arising from medication errors, drug abuse, misuse, off label use and from the use of biological medicines'*


• Lead NL with UK, SE
• Lead ES with DK
Signal detection
Signal validation; prioritisation
Signal assessment
Signals of special interest
• Lead DK with NL, SE
• Lead: UK with DK, ES, NL

Work Package 5 – Signal Management

- WP 5 – Best practice in signal management within the network of National Competent Authorities (NCAs)

  - *Focus on the NCAs and the work at national level in SM*
  - *Make the best use of the currently available tools*
  - *Identify best practices in MSs*
  - *Focus on practical aspects and opportunities to improve at NCA level*

What we want to achieve in WP 5

- ✓ Provide insights in the process of signal management in the European Union with a main focus on the national process
- ✓ Provide insights in available data sources and how to use them
- ✓ Clarification of terminology
- ✓ Provide insights in the process of signal validation and signal assessment
- ✓ Provide insight in the EMA/PRAC perspective of signal management
- ✓ Provide insights in the concepts and challenges for reports of special interest and possible approaches
- ✓ Show some practical examples

What has WP 5 done

Activities

- *6 F2F meetings (+1)*
- *Monthly teleconferences*
- *Survey of current SM practices (methods, tools, guidance) available in each MS + analysis*
- *Review relevant literature*

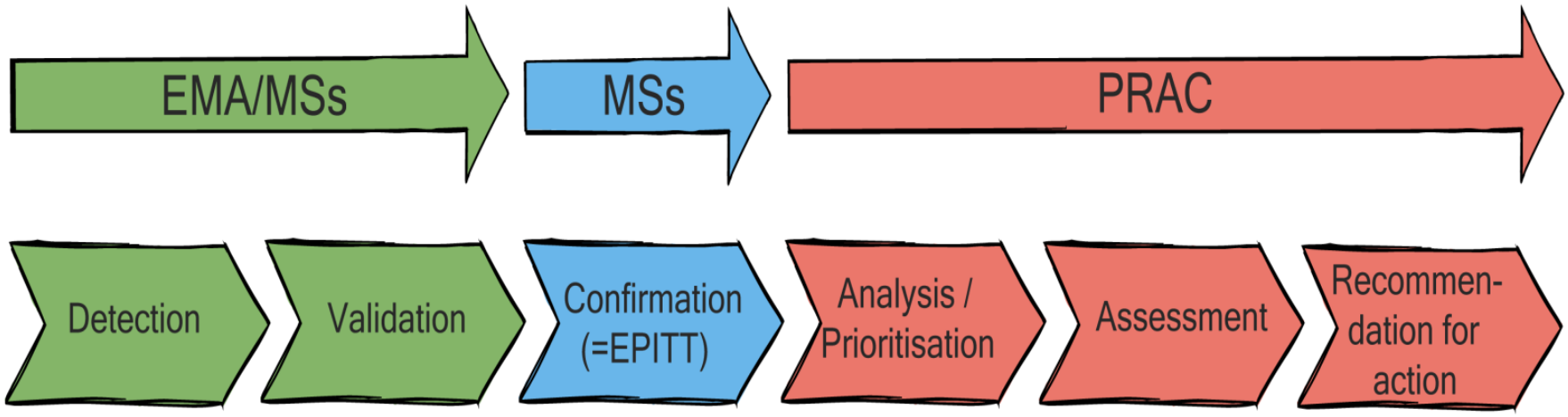
Output

- *Literature review*
- *Survey Results*
- *Pilot training*
- *Best Practice Guide*
- *Full training*
- *E-learning*

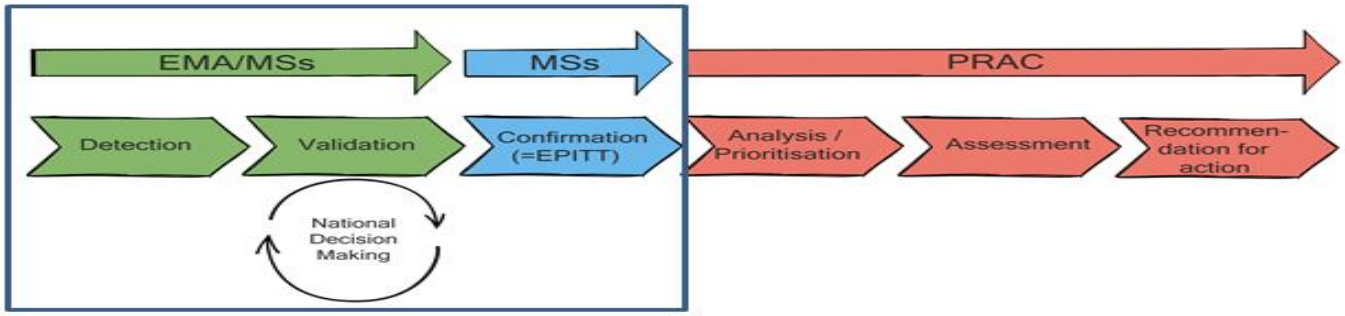
Where can you find the output of WP 5?

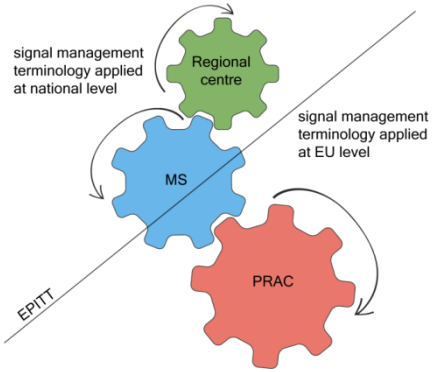
http://www.scopejointaction.eu

Signal Management
From Implementation to Operation



Introduction to the Process
Key Messages

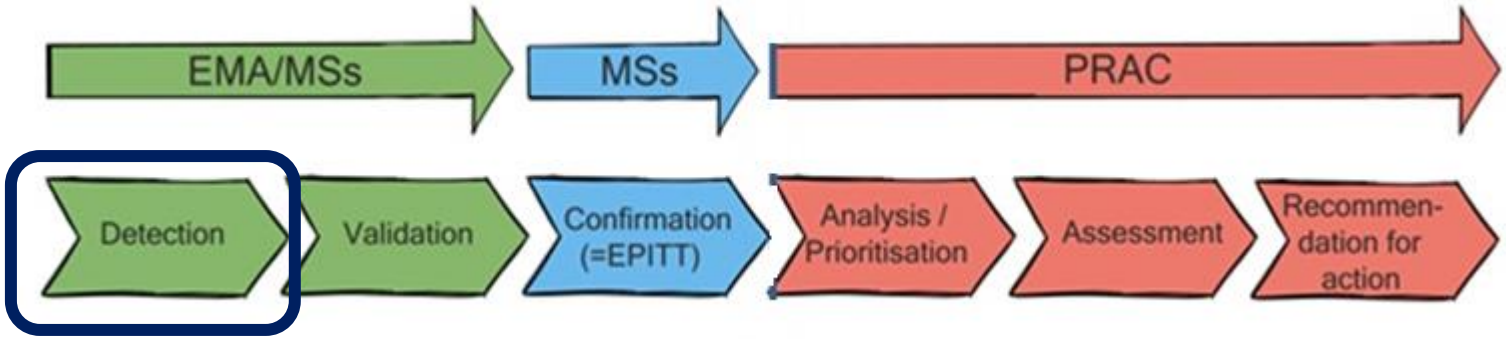




- ✓ Signal management definitions and processes might be different at national level. However, once a signal is entered into EPITT, the definitions as provided in the IR and GVP IX are applicable.
- ✓ Heterogeneity in the process is beneficial for the whole EU network
- ✓ Differences at NCA level allow the use of different methodologies and different levels of maturity of signals brought to PRAC
- ✓ The network can benefit from some consistency in the process

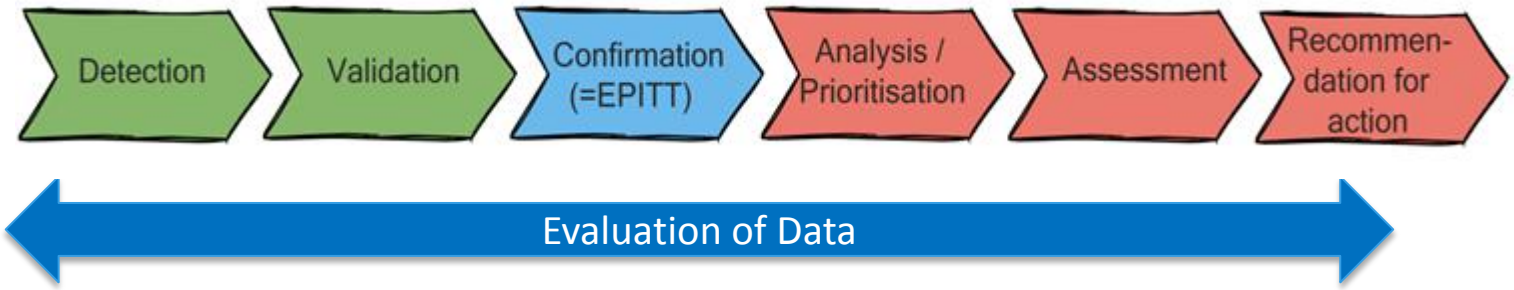
  E.g. minimum set of variables to be tracked, how to think about validation and confirmation etc.

Signal Detection
Key Messages



- ✓ Heterogeneity in the EU is valuable:
  - ✓ Diversity in databases and methodologies allows the detection of different signals in the different databases
  - ✓ Methods should fit the databases; for small databases, qualitative methods or simple rule-based methods are appropriate
  - ✓ The threshold and implementation decisions are more important than the method
- ✓ Focusing on serious events (DME, IME) is recommended
- ✓ Screening at PT level is recommended and can be complemented with screening at other (higher) levels of aggregation

Data Sources
Key Messages



Evaluation of data takes place at every step

The underlying reasoning is similar, but it varies depending on the aim of step and the data available

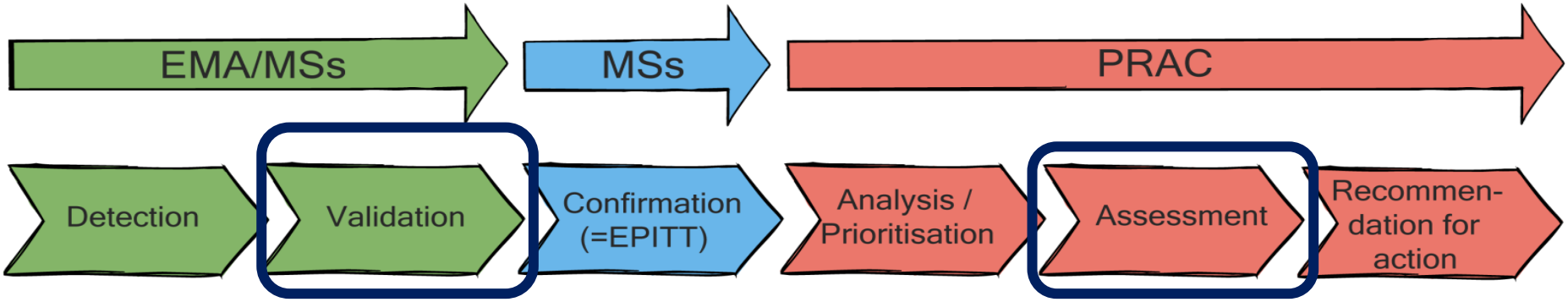
Many data sources available

Access to all of them is essential for assessors

Sound clinical judgement should be applied

Always on a case-by-case basis

Signal Validation and Assessment Key Messages



- ✓ Signal validation and signal assessment are different steps in signal management process, both involving evaluation of data
- ✓ They are different in the type of data to evaluate, in their aim, focus, and outcome
- ✓ A checklist can be useful for a consistent approach between different MSs
- ✓ It is important to know the roles of MSs, EMA and PRAC in each one of the steps

Signal Validation

Checklist

- ✓ Extra tool for assessors during validation, confirmation and assessment
- ✓ Not to be considered mandatory or exhaustive
- ✓ Important considerations to be taken depending on the step of the process and the extension of the evaluation of data
- ✓ Always expert clinical judgement needed

Signal Validation

Annex 2. Signal validation and assessment checklist

Validation of the signal

Important sources: SmPC, EPITT, PSUR, RMP, EMA website, other regulatory procedures

1. Is the event reflected in the SmPC of the active substance?
   i. For centrally authorised products, check the SmPC available at the EMA website; for nationally authorised products, check the SmPC(s) available in your MS
   ii. For active substances for which a generic version exists, check first the SmPC of the innovator product (if possible)

- Check sections 4.3, 4.4, 4.5, 4.6, 4.8, 4.9 of the SmPC for information regarding the event
- Check if the event might be covered by a similar term or a higher level term in the SmPC
- Check if the event is reflected in the SmPC of another medicinal product containing the same active substance
- Check if the event is reflected in the SmPC of a medicinal product from the same class
- In case of an interaction, you may check if there is information on the interaction in the SmPCs of the other medicinal products concerned

Signal Validation vs Signal Assessment

Validation

EMA/MS

Usually quicker and less extensive
Based on initial data that generated the signal
Aim: deciding if further data/analysis is necessary
Focus: new information? reasonable possibility?
Outcome: enter a signal in EPITT (or not)

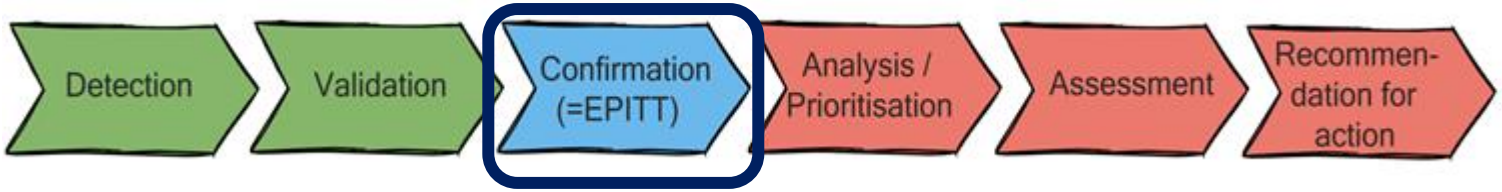
Assessment

PRAC Rapporteur /
Lead Member State

More extensive and thorough assessment
More data available for assessment
Aim: decide on regulatory action
Focus: definitive conclusion on causal association
Outcome: take a regulatory action (or not)

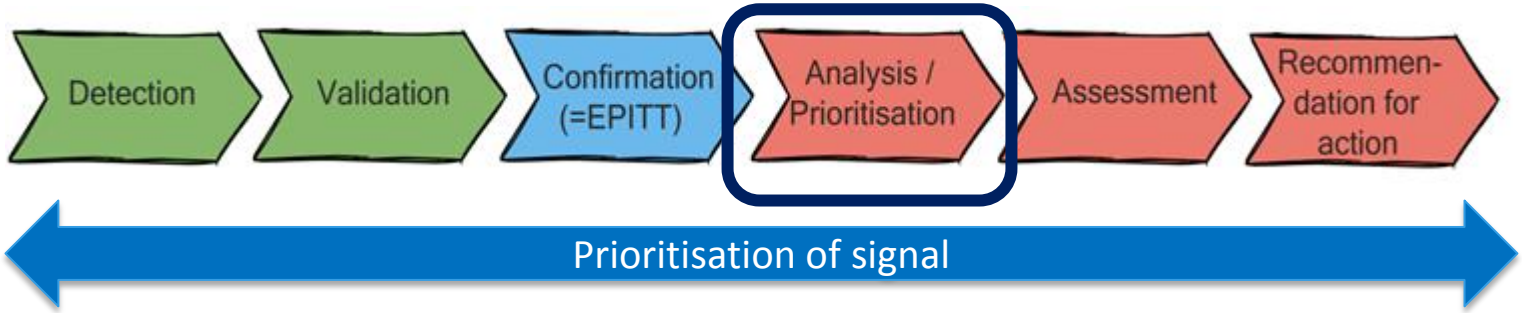
But they both involve evaluation of data

Confirmation
Key Messages



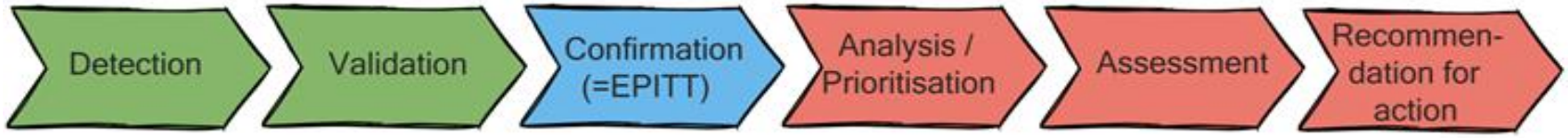
- ✓ Signal confirmation, based on the legal terminology, is a procedural step only relevant when a Member State wants to bring a signal to the PRAC agenda
- ✓ At the EU regulatory level, signal confirmation only refers to EPITT
- ✓ Lead Member State or PRAC rapporteur shall confirm/non-confirm a signal as soon as possible and within 30 days of receipt of a validated signal via EPITT

Prioritisation
Key Messages



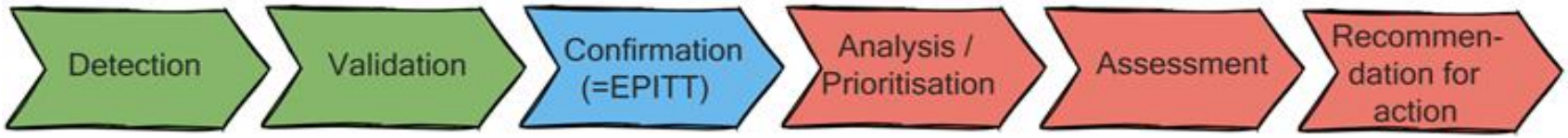
- ✓ Prioritisation happens at every step of the signal management process and is a continual activity
- ✓ We can use tools to reduce the subjectivity of reliance on individual judgment
- ✓ It is important to consider the following themes:
  - Public health implications
  - NCA obligations
  - Strength of evidence
  - Public perceptions

Reports of Special Interest
Key Messages



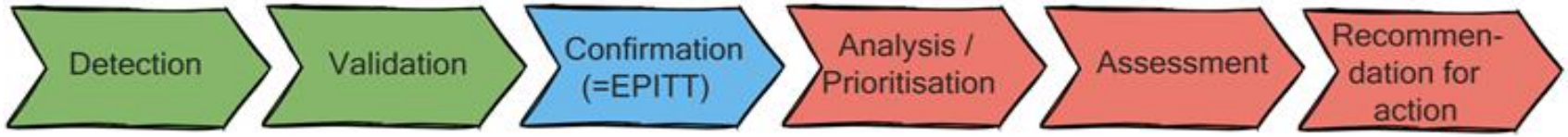
- ✓ Reports of special interest may warrant additional attention and different approaches for analysis. Qualitative assessment is often needed
- ✓ Resolutions to some of the difficulties in identifying reports of special interest
  - ✓ Population based approaches
  - ✓ Product/substance based approaches
  - ✓ Reaction based approaches
- ✓ Consider how the different approaches and concepts can be utilized in your own NCA
- ✓ Identify appropriate bodies to collaborate with and understand the importance of building effective relationships with them

SM at EMA/PRAC Level
Key Messages



- ✓ Insights in the workings of the PRAC, especially regarding the agenda, timing and transparency
  - ✓ When signals are discussed (silent/plenary)
  - ✓ Confirmation: Legal deadline 30 days from signal validation [art 21.3(a) IR)] To have it in the agenda for a specific month, should be confirmed by Friday, 10 days before PRAC
  - ✓ Communication of outcomes
  - ✓ Product information update |Translation of PRAC recommendations

E-learning



- Signal Management e-learning

http://walkgroveonline.com/scope_training/index.php

What we hope to have achieved

- More clarity on the concepts and the flow of the SM process in the EU
- Understand the concepts of **prioritisation, validation, confirmation, assessment** in the EU SM process
- Increase awareness regarding additional data sources and how to use them in signal management
- Gain some further insights in signal detection
- Awareness of existing supportive tools
- Awareness of possible approaches for reports of special interest to be used at national level
- Put into practice the knowledge acquired : real case scenarios workshop