EMA
EUROPEAN MEDICINES AGENCY

SMART Methods Working Group: Harnessing Collective Expertise to Strengthen Signal Detection

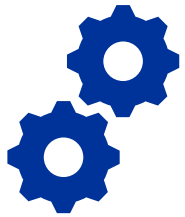
Review of main Achievements

Cosimo Zaccaria (EMA)

Signal Management Review Technical Working Group

Collaboration between Member States and EMA with the objective to strengthen and simplify the signal management process in the EU.

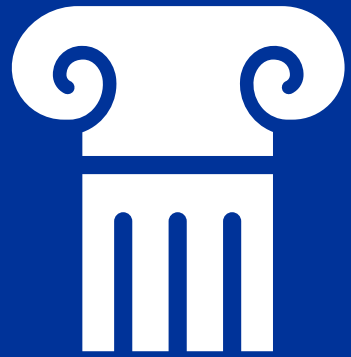
SMART PROCESS



- Evaluation of signal management processes essential for effective and efficient operation.
- Identification of opportunities for improvement and reinforcing elements that work well

SMART METHODS

- Leveraging expertise and review methods in signal detection
- Facilitate further collaboration with Signal Management Experts
- Highlight the International aspect of the Collaboration



- **continuous process evaluation,**
- **exploration of new methodologies**
- **enhanced transparency**

SMART Methods: Operational aspects

Meetings and Participation

- Quarterly meetings
- Reports to PRAC on a quarterly basis
- Interaction with other forums
- Tracking tool and monitor progress & deliverables

https://www.ema.europa.eu/en/committees/working-parties-other-groups/signal-management-review-technical-smart-working-group

Co-chairs:

- **E. van Puijenbroek (Lareb)**
- **C. Zaccaria (EMA)**

Members

- **28 NCAs members**
- **12 EMA members**
- **4 WHO-UMC members**
- **2 academic centres**
- **1 Independent Experts**

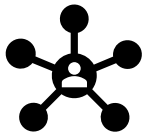
SMART Methods Objectives

- **Leveraging** the group resources and its on-going initiatives
- Promoting **Interaction** with other forums
- Managing a **portfolio of initiatives** with different levels of engagement

Prioritise research areas

Review and Test new Methods

Validate and Implement Evidence-base methods



Communicate to ensure knowledge transfer

Key Drivers:

- **Ease of Development**
- **Ease of implementation and maintenance**
- **Ease of interpretation of results**
- **Significant impact on the overall process**

Some important achievements

eRMR implementation

- Priorities and format
- Subgroup analysis
- Screening fatal cases
- Unexpected increase in frequency

Signal detection Vulnerable Population

- Paedi. TMEs/RORs
- Geriatric ROR
- Pregnancy algorithm

Covid19 Enhanced Monitoring

- AESIs (vTMEs)
- O/E analysis
- Restricted ROR
- Dashboards
- Masking Effect

Role of AI in Signal detection

- Eureka
- Automatic case adjudication for TTS

Others

- Mec. of action in SD
- Opioid use (monitoring risk factors)
- Impact of Non Serious Reports

Established Priorities

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

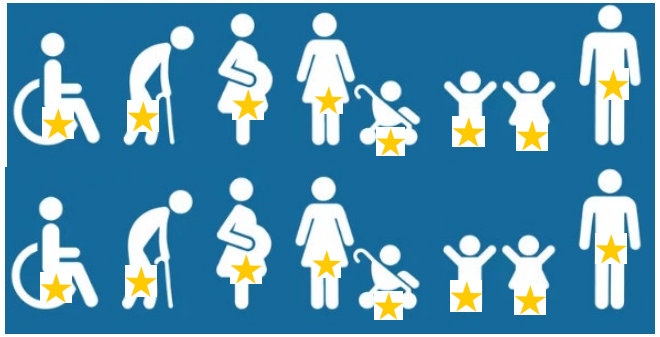
Screening for adverse reactions in EudraVigilance

- ***SafetyNet:*** *Support prioritisation of MedDRA Terms that are likely to be drug attributable: Designated Medical Events (DMEs) / Adverse Events of Special Interest (AESIs)*

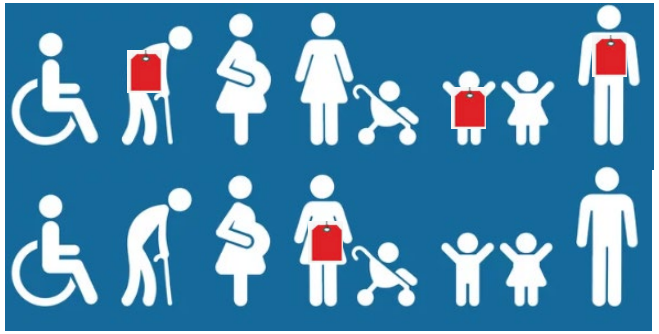
- ***Signal Of Disproportionate Reporting:*** *Support automatic screening based on statistical tools*

- ***Weekly screening*** *of recent publications*
- *Review of safety communication from other jurisdictions*

Reduce time to detection



Control False Positives



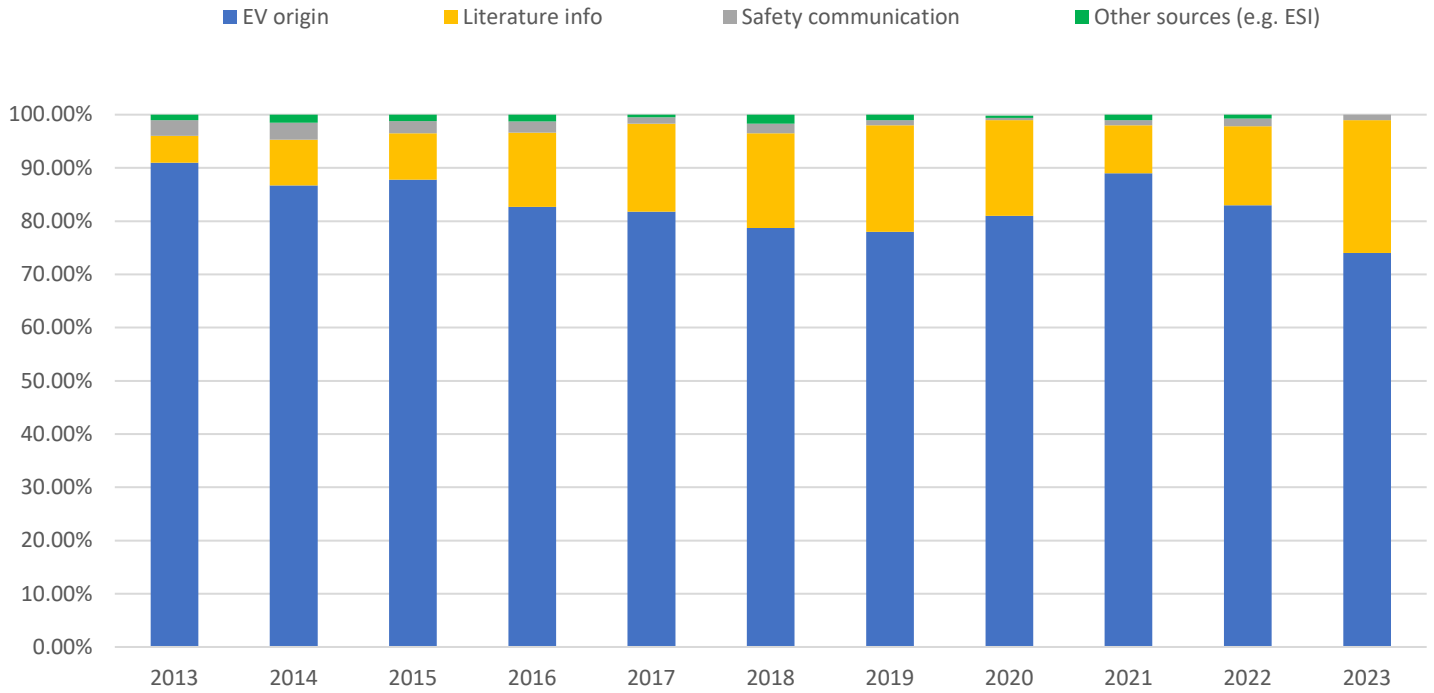
Complementary activity

EMA

Relevance of data sources

Origin of the reviewed Signals

- EV remains the main data source



- Spontaneous data remain the most valuable source of information for signal detection
- Literature screening increasingly important over time
- Combinig data sources provides a more complete and reliable picture of emerging safety issues.

Workplan 2022-2025: Status

Completed Ongoing Not started

Scoping

defining objectives, potential methods & resources to be used

- Statistical Correction of Uncharacterised Bias (SCRUB)
- SMART Website

- Mechanism of Action (Drug-ADR Causal pathways)
- SSA

Further Exploration

expanding on initial findings, literature review for new hypotheses, investigate gaps and gain more insights

- Time-Series forecasting
- Pediatrics
- Geriatrics
- Abuse/Misuse of opioids
- MedDRA synonymous: Terms other than standard MedDRA for signal detection
- Drug interactions
- RWE for signal detection

Experimentation

design and execute tests to validate/reject approaches for implementation

AI Adjudication of cases

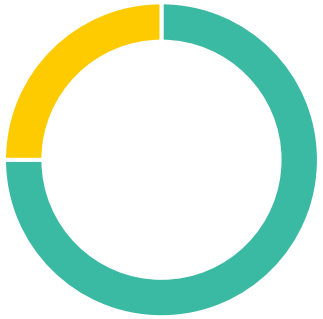
Signal Analytics (MNEMOSiNE)

Reference Dataset (EurEKA)

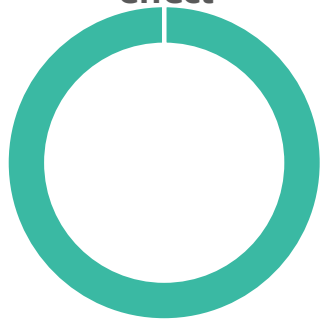
Priorities

ranking of research topics according to their importance, urgency and relevance

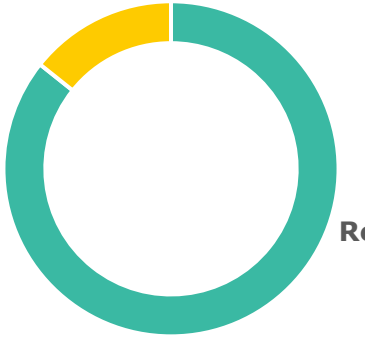
Observed to Expected



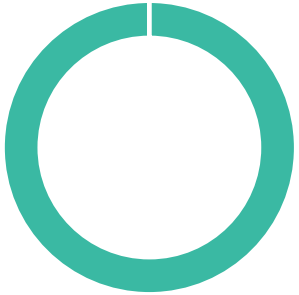
COVID-19 Masking effect



Pregnancy algorithm



Report clustering based on ADR profile



Lessons Learned on Observed-to-Expected Analysis Using Spontaneous Reports During Mass Vaccination

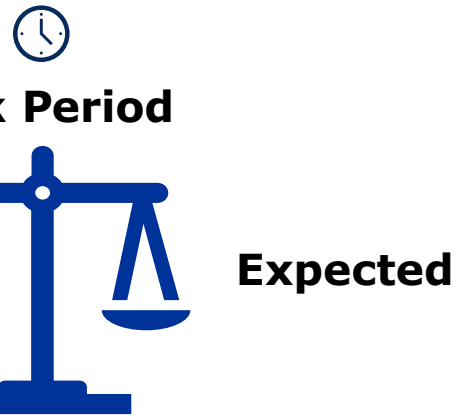
María Gordillo-Marañón[1,2] · Gianmario Candore[3] · Karin Hedenmalm[1] · Kate Browne[4] · Robert Flynn[1,5] · Loris Piccolo[1] · Aniello Santoro[6] · Cosimo Zaccaria[6] · Xavier Kurz[1]

Objectives

- Define strategy to generate rapid evidence on AESIs for signal contextualisation

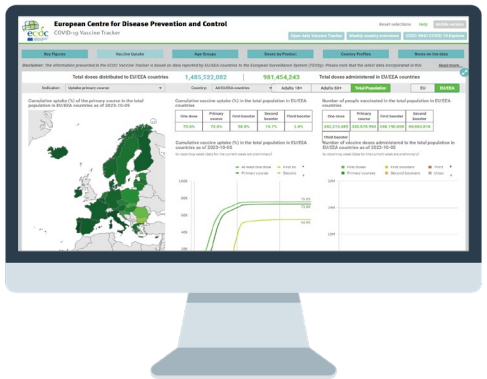
Deliverables

- ☑ Forthnightly routine analyses shared with the network
- ☑ Descriptive analysis to improve coding terms and risk periods
- ☑ Publication of lessons learned



Methods:

- Collect coverage data stratified by age and gender
- Define MedDRA strategy and coding
- Generate BGRs stratified by age and gender
- Compare observed data with expected



Key Aspects

- Understand strenghts and limitation of this methodology
- Stratification and coding terms are critical
- Guidance updates

Masking Effect of Covid 19 vaccines

Objectives

- Assess the magnitude of the over-representation of Covid19 vaccines in EV
- **Deliverables**

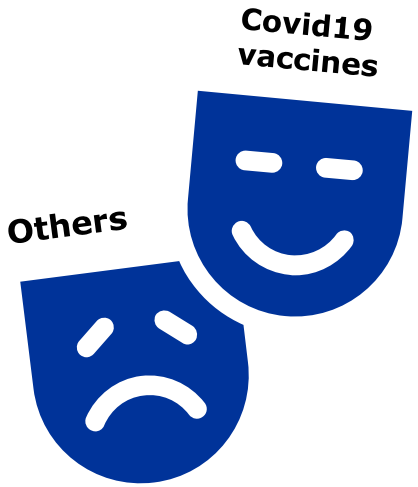
☑ Create focus group

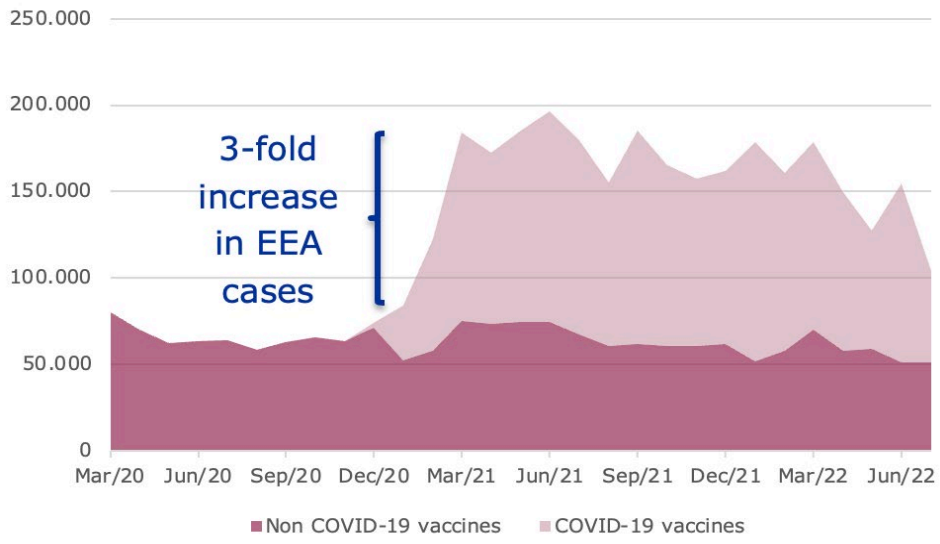
☑ Impact assessment

☑ Propose remediation strategies and easy to implement methods

Methods:

- Impact analysis using influential outliers
- Removal of Covid19 vaccines from ROR calculation
- Imbalance analysis between competing vaccines





Key Aspects

- Impact in small databases can be significant
- Impact on large databases is more moderate
- Alternative prioritisation approaches in signal detection can minimise this bias.
- Remediation approaches:
  - Identify most impacted events
  - Remove covid19 vaccines from denominator

Identification of Pregnancy Adverse Drug Reactions in Pharmacovigilance Reporting Systems: A Novel Algorithm Developed in EudraVigilance

Cosimo Zaccaria[1] · Loris Piccolo[1] · María Gordillo-Marañón[2] · Gilles Touraille[1] · Corinne de Vries[1]

Objectives

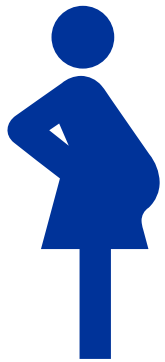
- Identify data elements that are likely to hold pregnancy information in ICSRs and develop an algorithm

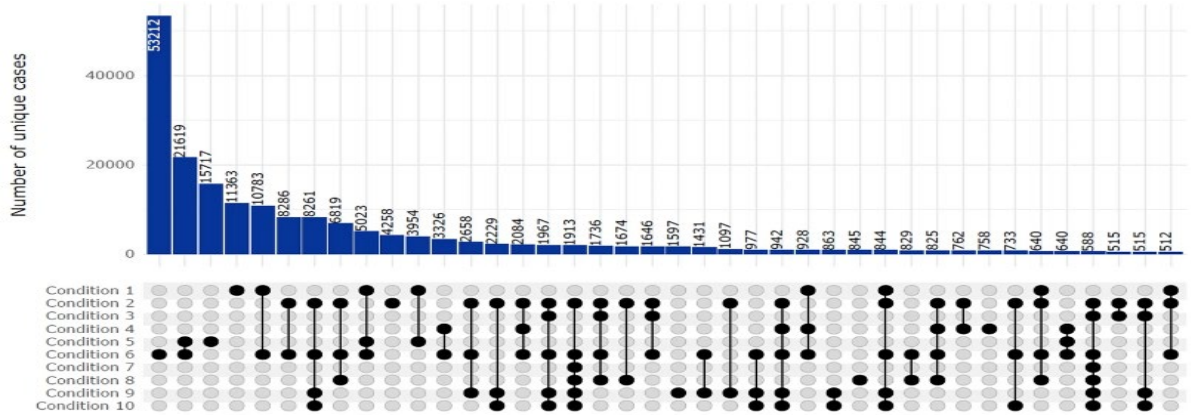
Deliverables

- ☑ Create a focus group
- ☑ Publish the algorithm
- ☑ Implement the algorithm in EVDAS + Dashboarding
- ☑ Support GVP Pregnancy and Breastfeeding

Methods:

- Validate the algorithm (90%PPV) against the SMQ ' Pregnancy and Neonatal Topics' (54%PPV)
- Compare EMA algorithm with other existing algorithm





Key Aspects

- Co-reporting 'maternal exposure during pregnancy' and Route of Adminsitration : transplacental is important to improve data retrieval
- The algorithm is focussed on ADR during pregnancy to further supports signal detection activities

Leveraging 20 years of EMA signal records: An overview of drug interaction signals with MNEMOSiNE

Maria Mantziri[1], Elpida Kontsioti[1] Julie Durand[1], Viola Macolic Sarinic[1], Cosimo Zaccaria[1]

Objectives

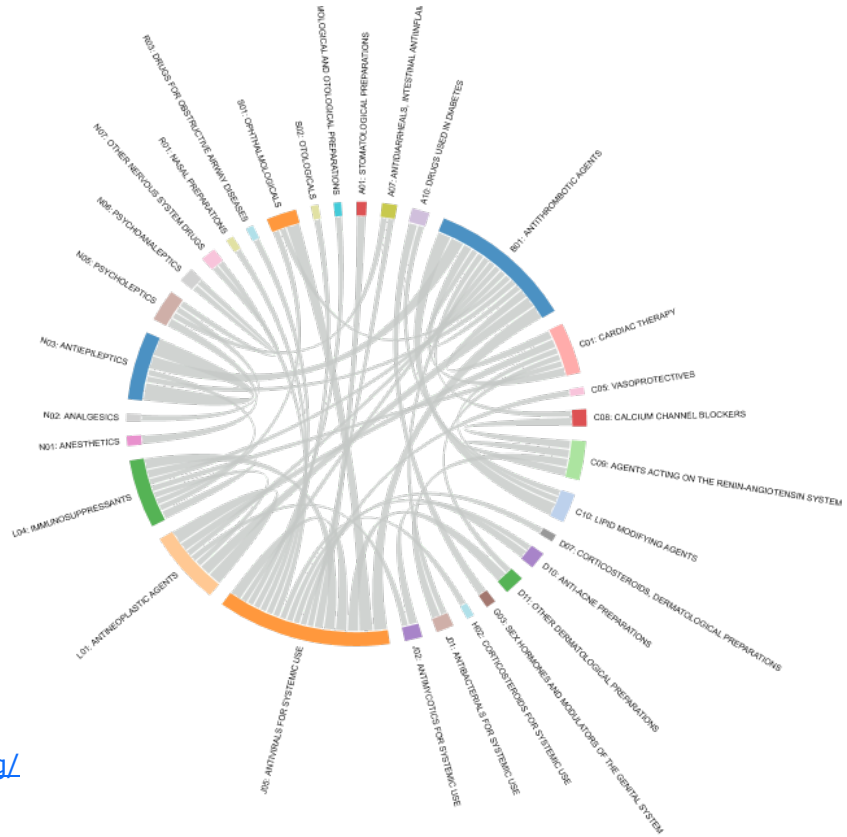
- Describe DI signals in Mnemosine (historical knowledge from 27k EMA reviewed signals)

Deliverables

- ☑ DI signals were identified and described
- ☑ Use of Mnemosine as an asset to generate insight on DI signals

Methods:

- Extract DI signals from 2004-2023
- Review regulatory outcomes of DI validated signals



Key Aspects

- Literature remains key for detecting DI signals
- Majority coded as general medical events or general interaction complicating mechanistic interpretation
- Further SD efforts may benefit from incorporating biological and omics data

Poster presented at the ISoP Cairo 2025 https://isop2025cairo.org/

Geriatrics

Objectives

- Identify elements that might be used to strengthen the prediction of highly age specific effect

Deliverables

☑ Implementation of relative geriatric ROR in eRMR

Paediatrics

Objectives

Identify elements that might be used to strengthen the prediction of paediatric ADRs

Deliverables

☑ Creation of paediatric Targeted Medical Events TME list

☑ eRMR Implementation of paediatric TMEs

☑ Implementation of relative paediatric ROR in eRMR

❑ Further validation of TMEs list is needed

Potential New Opportunities

- New insights from AI
- Leverage DDIs algorithms
- Leverage RWE
- Provide input to GVP

Abuse/Misuse/Med. Error/Overdose

Objectives

- Assess new methods for better monitoring

Deliverables

- ☑ Descriptive analysis on overdose, medication error, abuse and misuses in EV with opioids
- ❑ Propose routine reports of monitoring of opioid trends

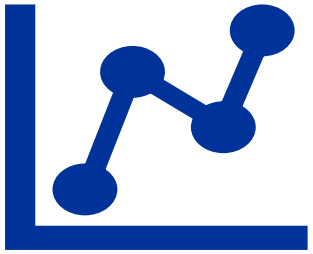
Time-Series Analysis

Objectives

- Create a model to detect unexpected increases in frequency UIF
- Validate the tool

Deliverables

- ☑ Validation of the tool & Publication
- ❑ Further prospective validation



An algorithm to detect unexpected increases in frequency of reports of adverse events in EudraVigilance

Luis C Pinheiro [1,✉], Gianmario Candore [1], Cosimo Zaccaria [1], Jim Slattery [1], Peter Arlett [1]

Potential New Opportunities

- Advance technologies
- AI for pattern identification

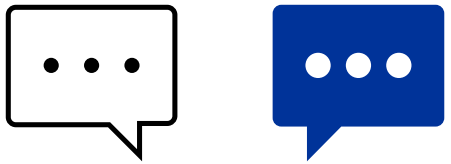
MedDRA Synonymous

Objectives

- Test methods to identify groups of terms other then standard MedDRA hierarchy for statistical SD

Deliverables

- ☑ Consider UMC work on vector representation of AE
- ❑ Prospective validation of the tool for implementation



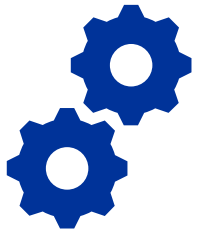
Mechanism of Action

Objectives

- Identify pathway elements that might be used to predict ADRs

Deliverables

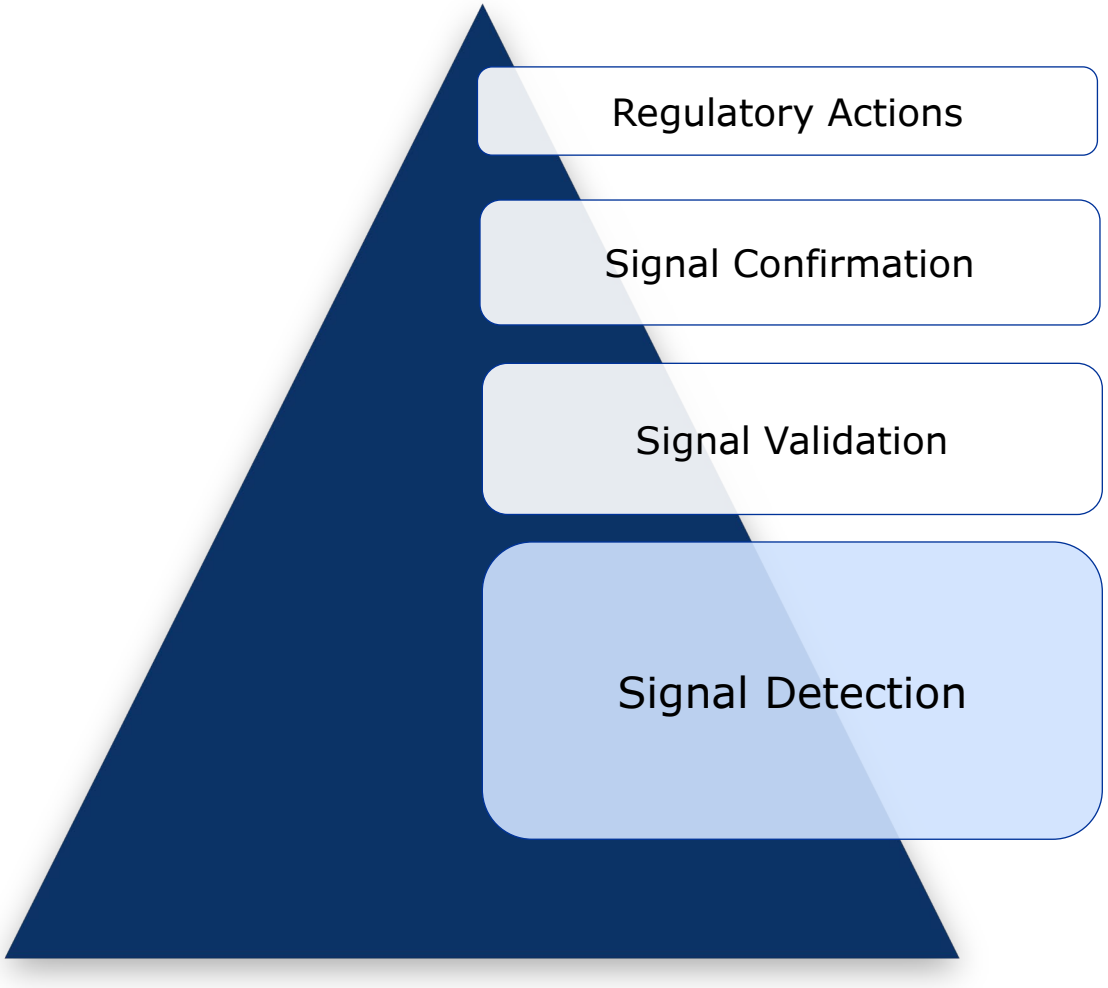
- ☑ Identify sources of data
- ❑ Prediction models to be tested



Potential New Opportunities

- Advance technologies
- AI for pattern identification

Key Performance Metrics in Signal Detection



Regulatory action Rate / Publications /Guidelines:

Assess ability to mitigate risks and respond quickly to emerging issues and overall efficiency in the signal detection process

Quality of Individual cases reviewed

This metric, together with the n ADRs screened and signals reviewed, reflect the overall workload and quality of reports

Average of individual cases reviewed to validate a signal

This metric reflect the overall complexity in the signal validation process

Time to Detection from first report received / flagged as a priority

This metric provides insight of the effectiveness of signal detection

Feedback from SMART Methods Members

Smart Input

Current Focus

Priorities

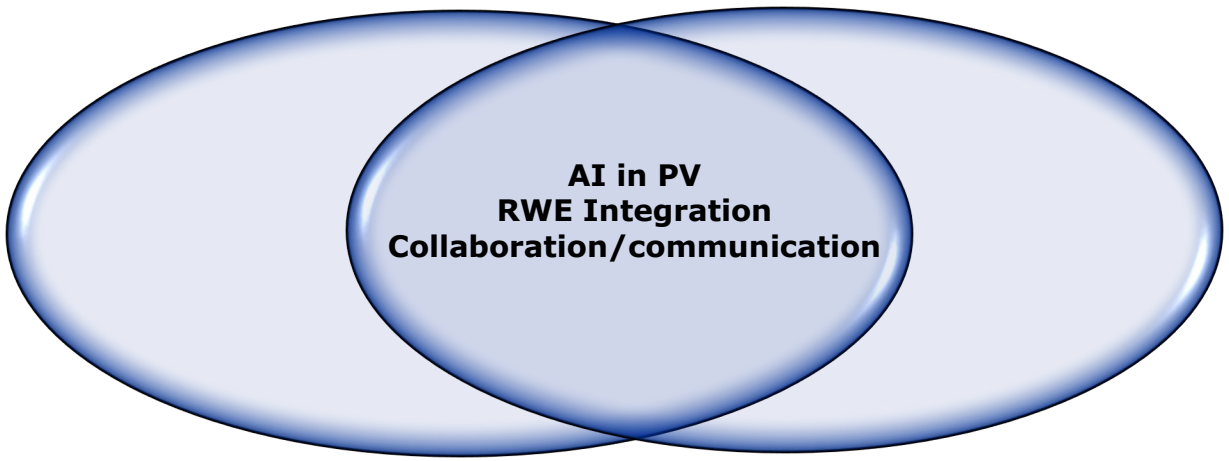
Support

Feedback

Learnings

Collaborate

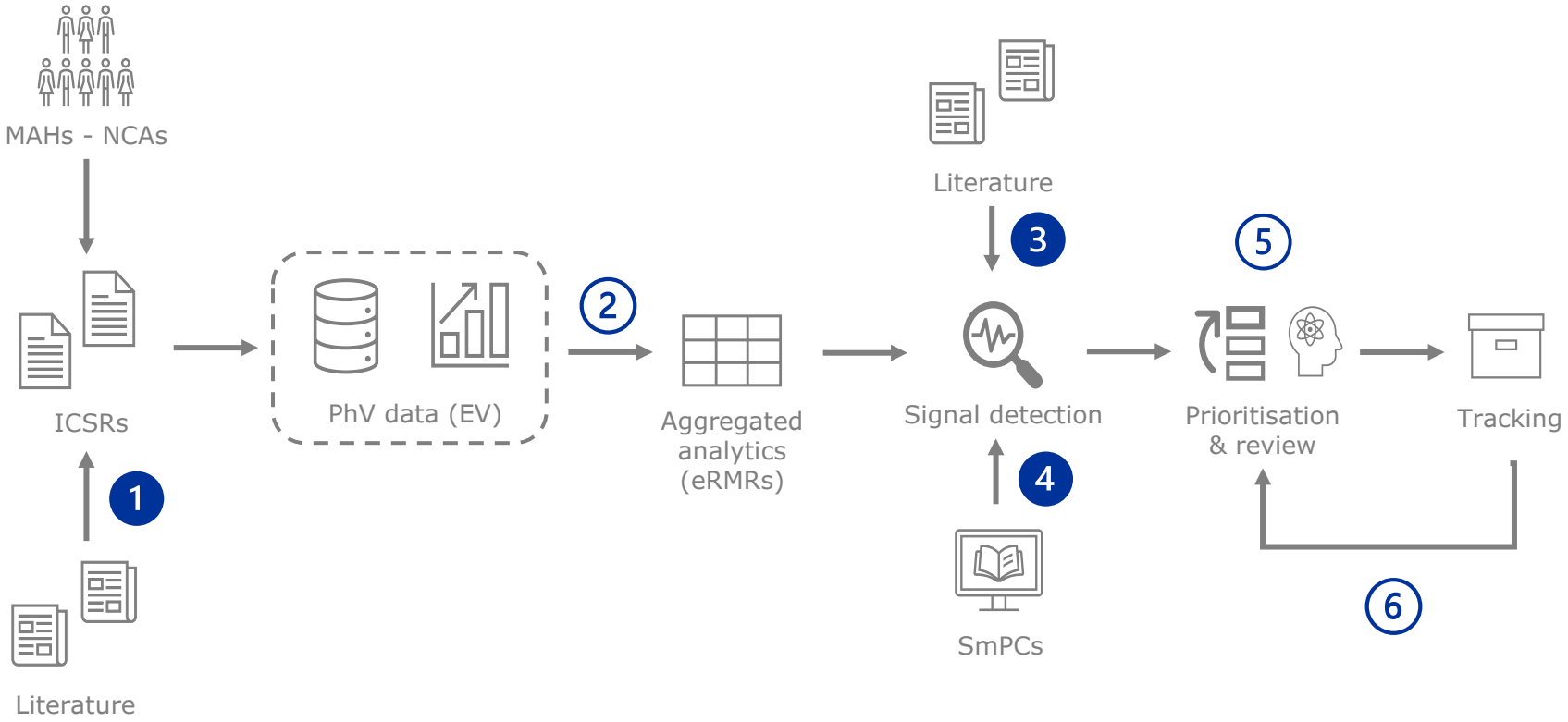
Improve



FUTURE AREAS TO PRIORITISE

1. **Responsible Use of AI in PV**
2. **Better integration of RWE**
3. **Better Collaboration, training and Communication**

Use of AI and automation in EMA signal detection workflow



Internal Digital Innovation Team (HDL)

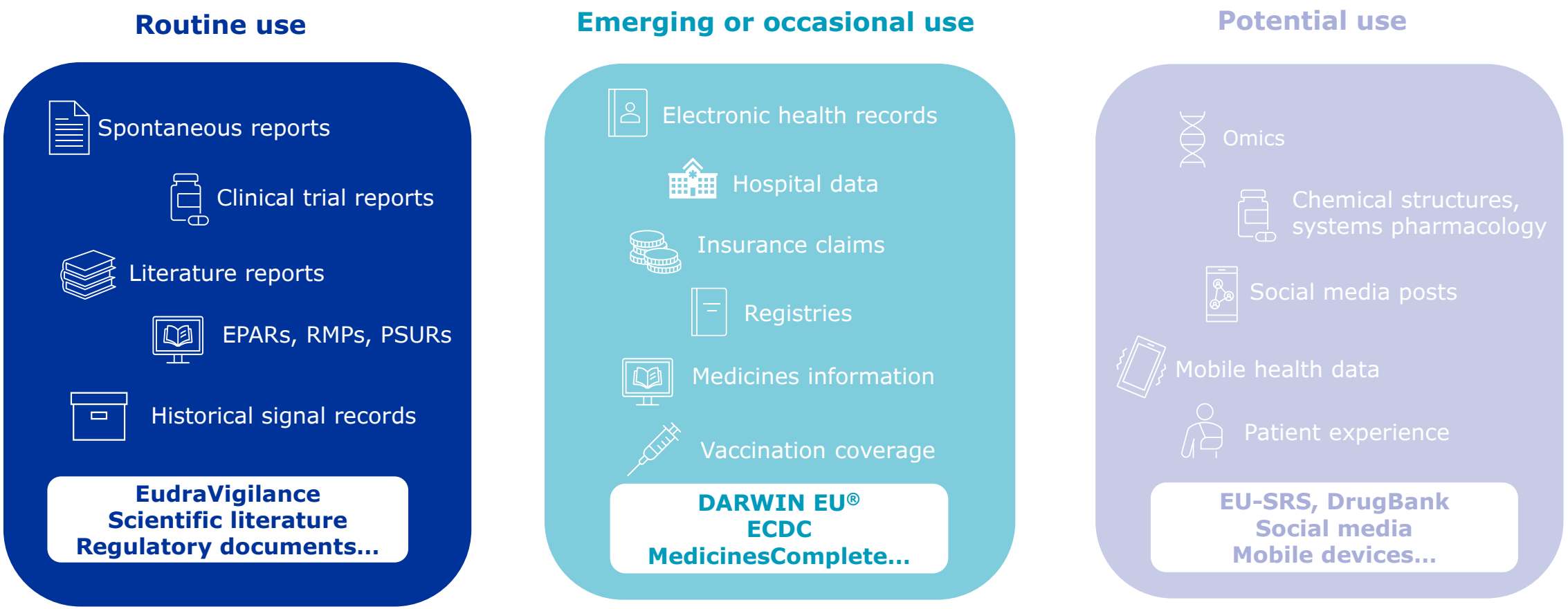
Projects

1. Literature screening for ICSRs (OWLS)
2. eRMR production
3. Literature screening for signals (ERATO)
4. ADR data extraction (EurEKA)
5. AI-enhanced case adjudication (AERGIA)
6. Insight generation from historical reviews (MNEMOSiNE)

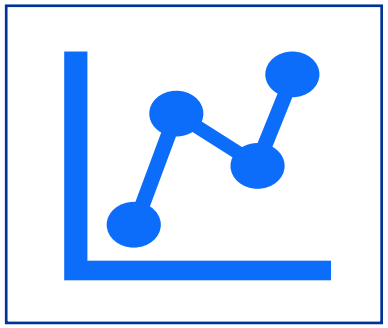
Status

- ● (Pilot-)deployed
- ○ Ongoing / upcoming

Integration of Other Data Sources



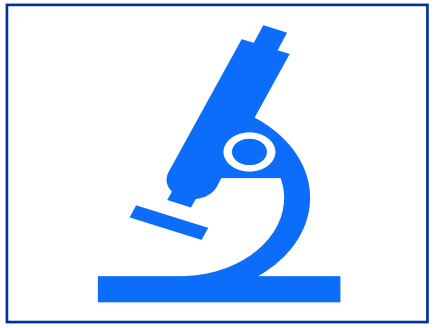
Final remarks



Research Achievements

Crucial Role of SMART in reviewing and implementing a wide range of emerging methods

Covid-19 pandemic has created an unprecedent need for methodological standards and fast generation of high-quality evidence to support regulatory and public health decision-making



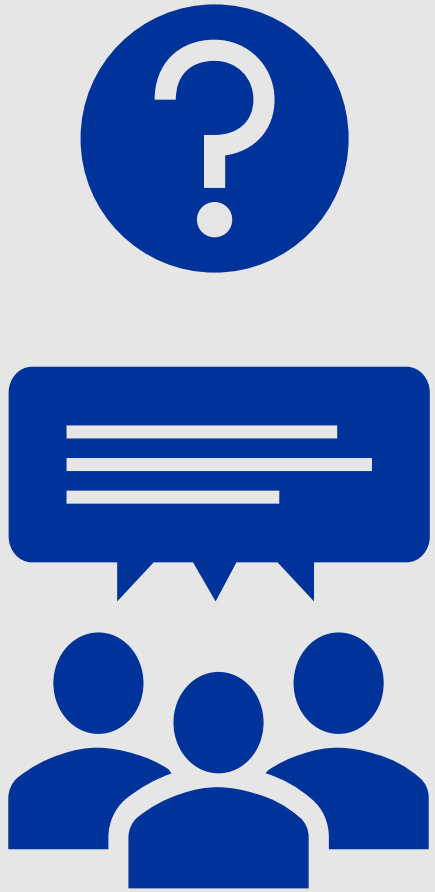
New Opportunities

Leverage AI in Pharmacovigilance

Integration of RWE for signal contextualisation

Facilitate both bilateral and multilateral collaboration to accelerate progress

Collaborative effort: transforming Data Into Tangible Public Health Outcomes



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Thank you

Follow us