CMO&PS

Risk Management Systems in Pharmacovigilance

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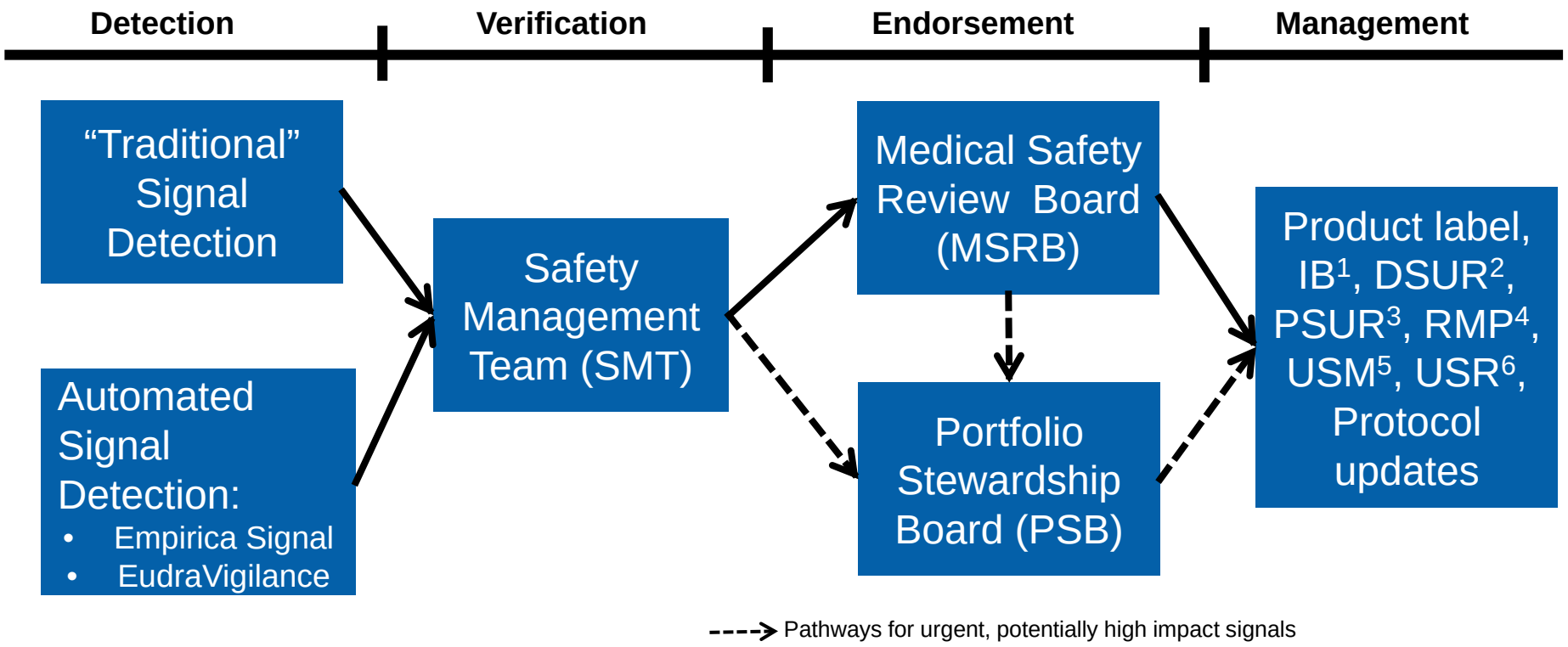
Risk Management System Governance

From Detecting Safety Signals to Managing Safety Risks



[1] Investigator's Brochure | [2] Drug Safety Update Report | [3] Periodic Safety Update Report | [4] Risk Management Plan | [5] Urgent Safety Measure | [6] Urgent Safety Restriction

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What is a Safety Signal?

- Definition of a safety signal (EMA Guideline on good pharmacovigilance practices (GVP) Annex I - Definitions (Rev. 4))

> Information arising from one or multiple sources, including observations and experiments, which suggests **a new potentially causal association**, or a **new aspect of a known association** between an intervention and an event or set of related events, either **adverse or beneficial**, that is judged to be of sufficient likelihood to justify verificatory action.

- Therefore, a safety signal is:
  - ✓ **Hypothesis generating** only
  - ✓ But **not** a **confirmed risk**

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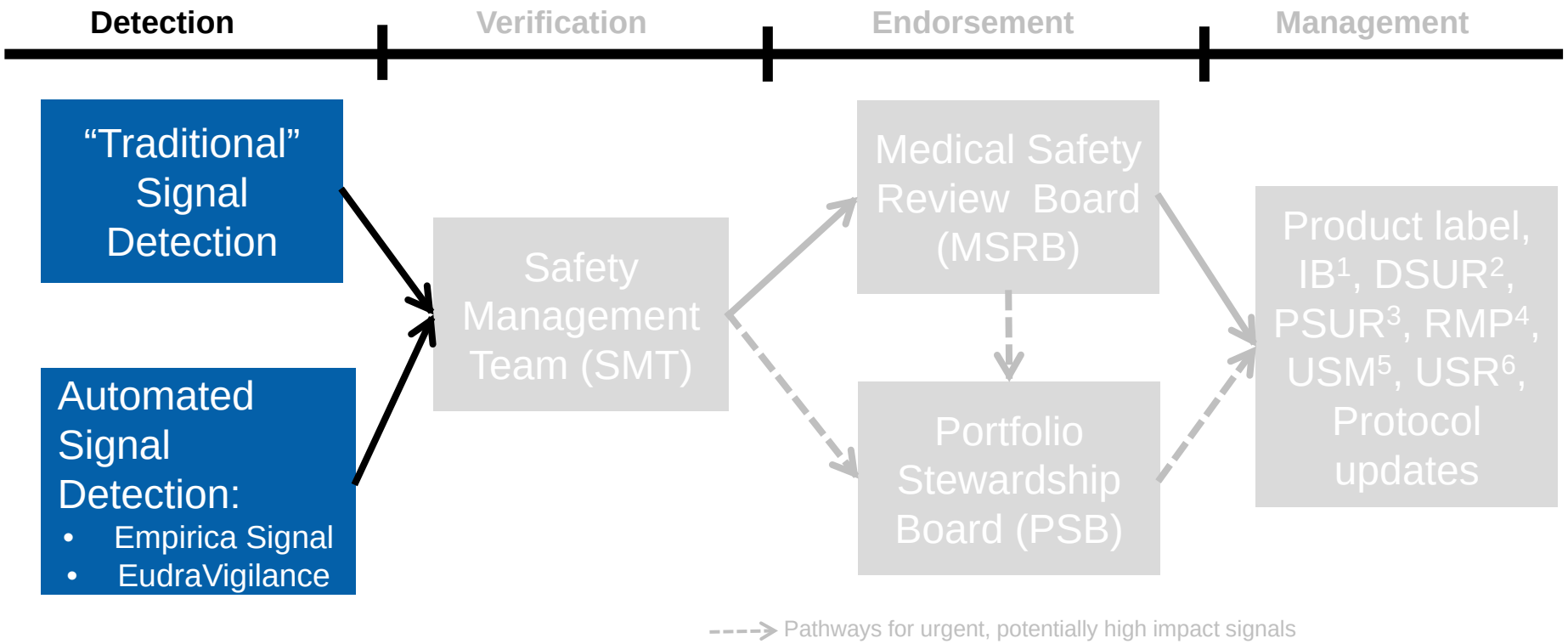
Sources used for Signal Detection



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Hybrid model of traditional and automated signal detection

Traditional signal detection (at pre- and post-marketing stage)

Internal:

- Preclinical & Human studies
- Individual case safety reports database (ARGUS)
- Literature
- Class effects / Mechanism
- Product quality issues

External

- Health Authority (including regulatory information)
- WHO-UMC
- Literature

Automated signal detection (only for marketed products)

Empirica:

- All post-marketing Argus cases (both serious and non-serious) from
  - Spontaneous reporting
  - Literature
  - Patient Oriented Programs (POP)/ Patient Support Programs (PSP)

Eudravigilance:

- GVP IX Revision 1 & Addendum
- Access to the electronic Reaction Monitoring Report (eRMR)
- Drug Event Combinations (DECs)
- In addition to Empirica

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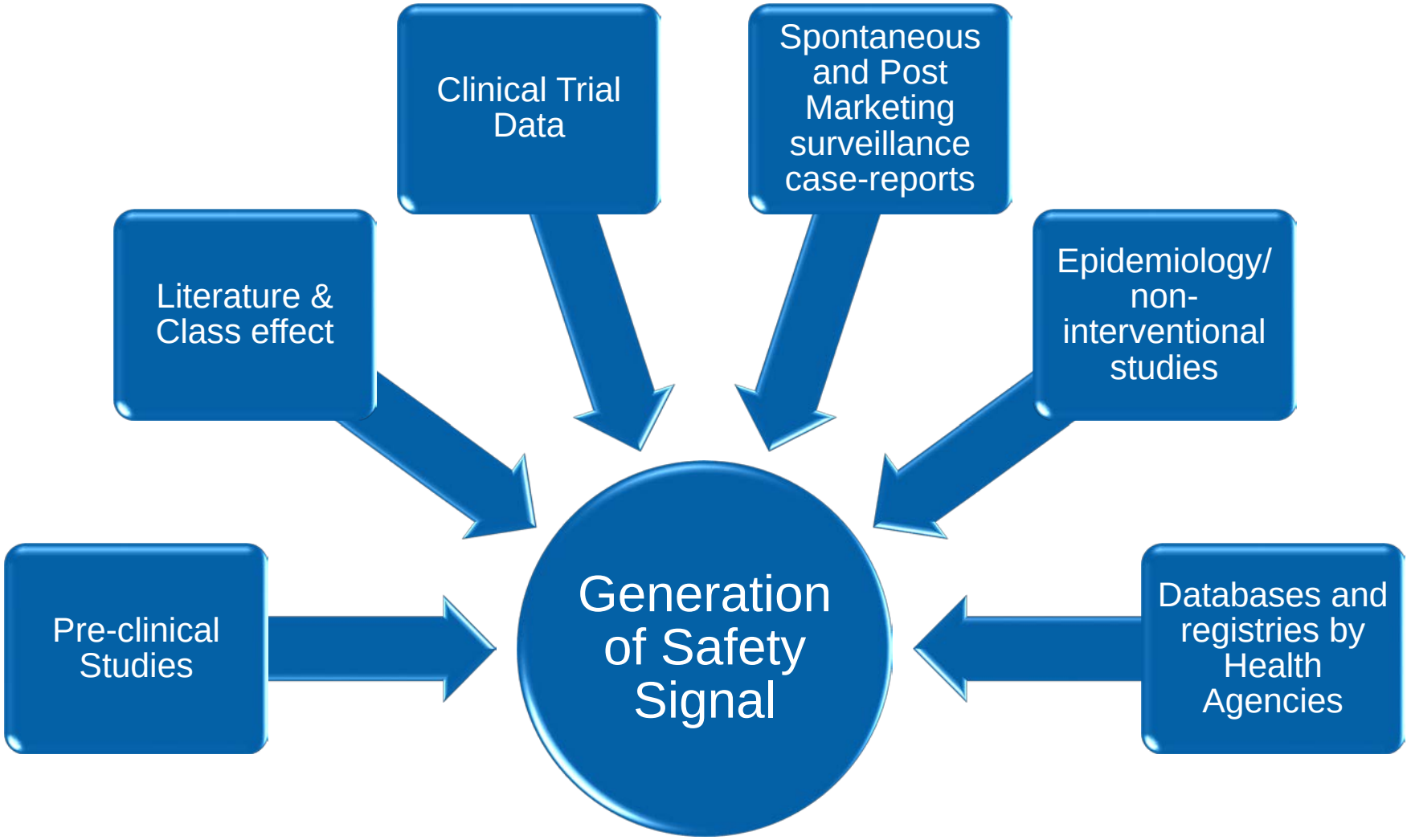
Traditional Signal Detection

Applied throughout a product's lifecycle



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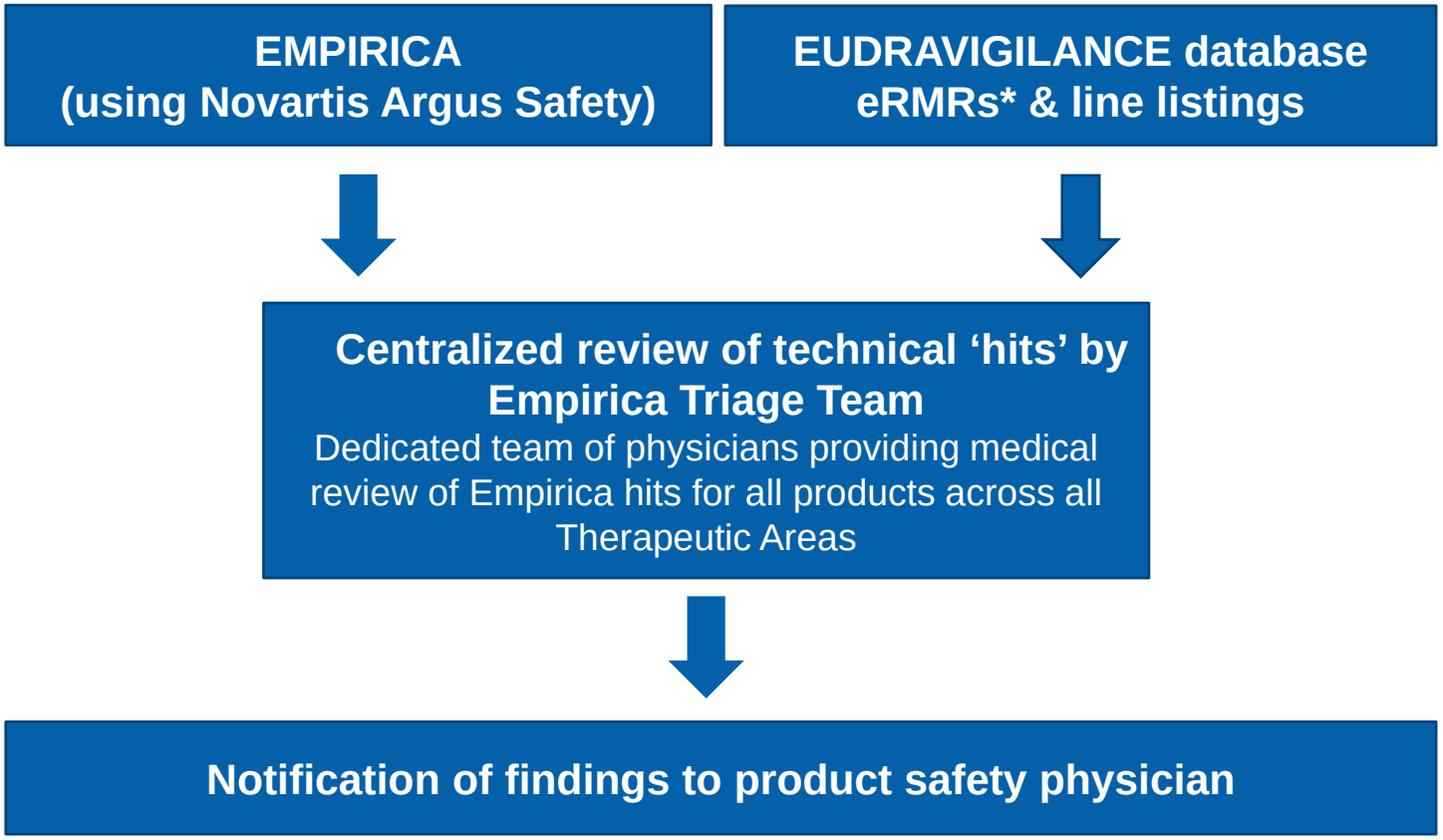
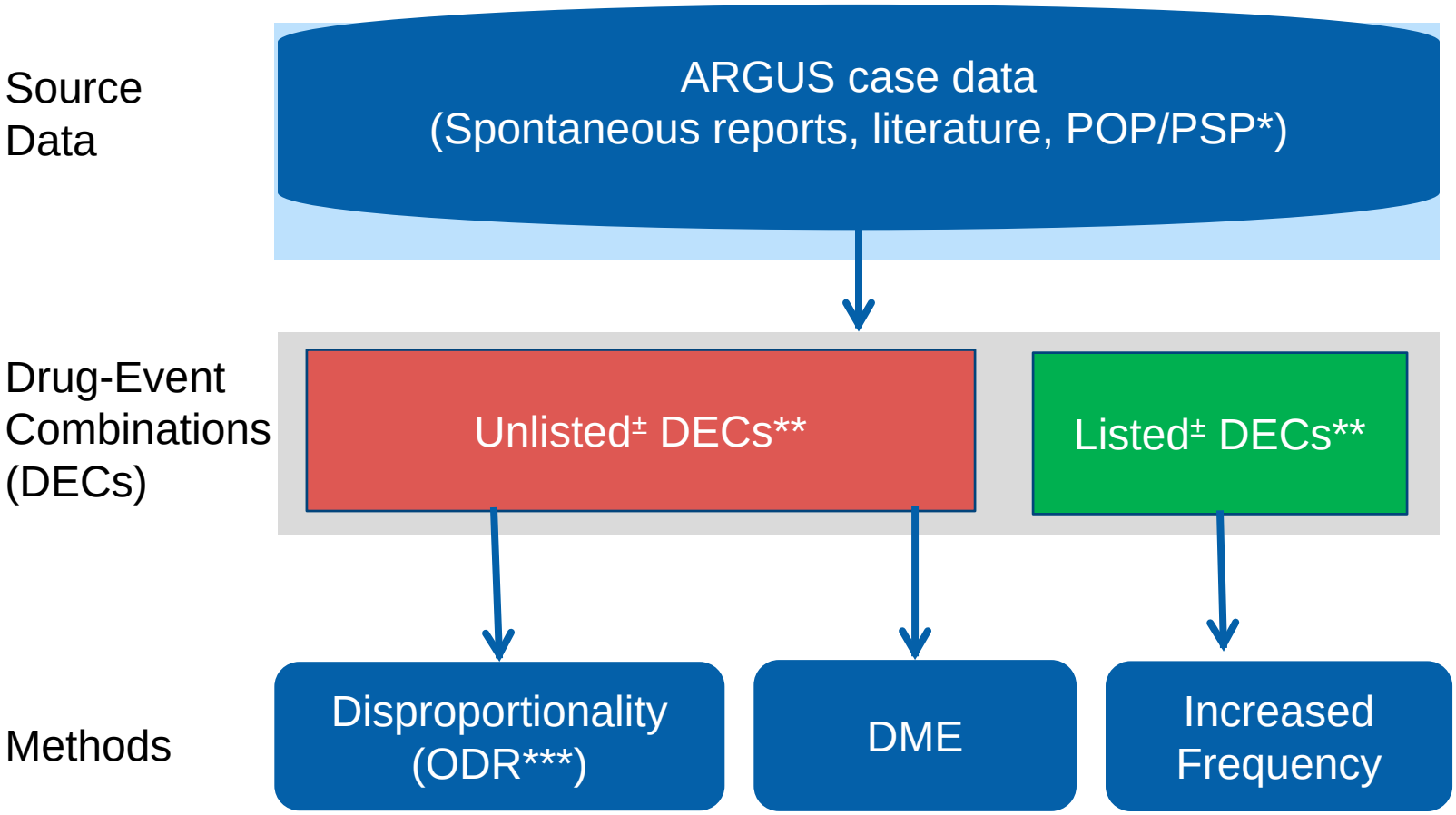
Automated Signal Detection

Overview



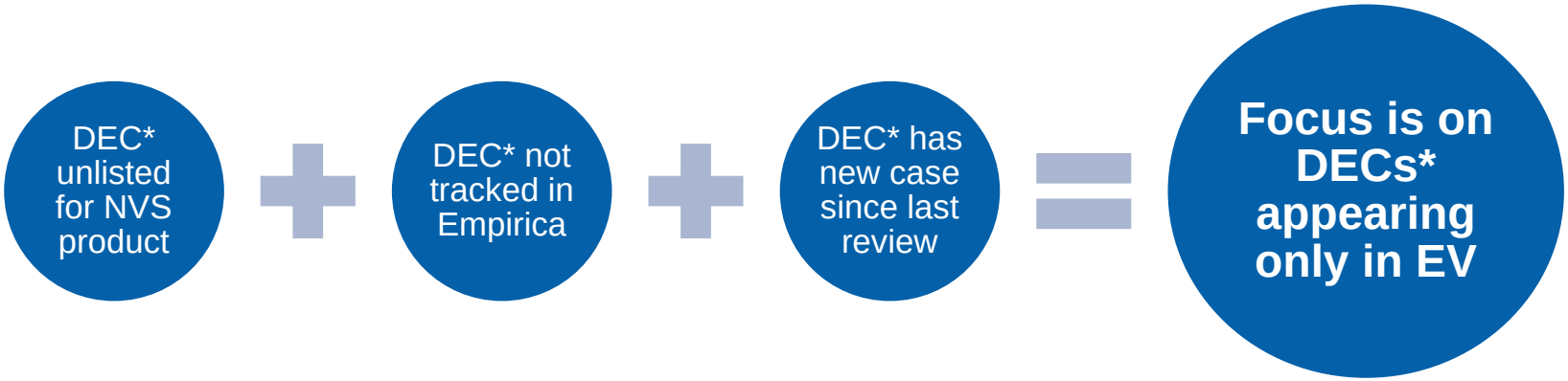
* electronic Reaction Monitoring Report

Empirica Signal Detection Method



* Patient Oriented Program / Patient Support Program
** Drug Event Combination
*** Observation of Disproportionate Reporting
± Listedness assessed against Company Core Data Sheet

EudraVigilance signal detection using eRMR



* Drug event combination
** Signal of disproportionate reporting

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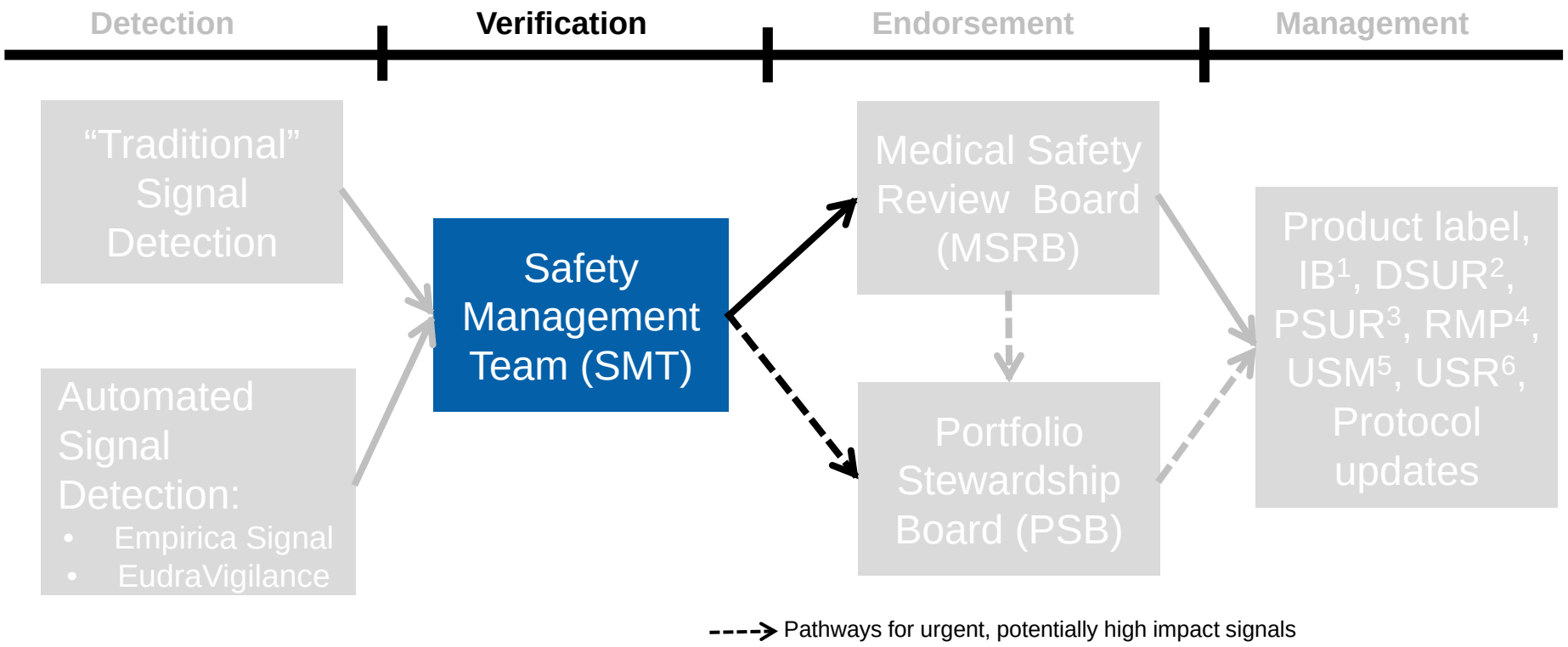
Signal validation, analysis and assessment



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Safety Management Team (SMT)

Overview

Mission

- Conduct a regular comprehensive review of safety information from available sources to evaluate, identify and escalate new safety signals with the objective of minimizing risk for patients receiving Novartis products

Composition

- **Cross-functional team** representing a sub-team of the Global Project Team/Global Brand Team
- Meets at least quarterly

Objectives

- Responsible to ensure the review of all available safety information for the **identification and validation of new risks** from signals as well as for the ongoing evaluation of identified and potential risks and topics of special safety interest for evidence of increasing severity, specificity or frequency

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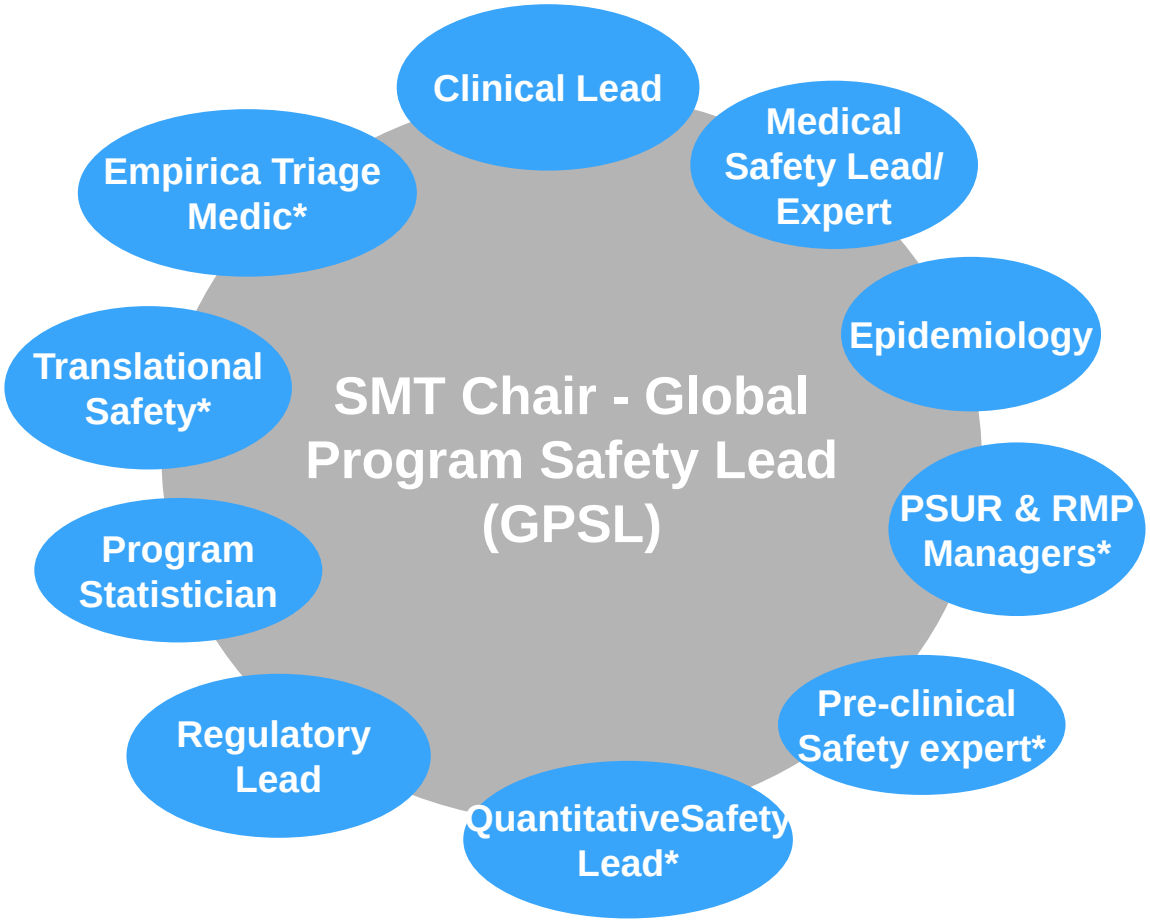
Safety Management Team (SMT)

Composition



* If applicable

Safety Management Team (SMT)

Objectives – moving from signals to risks

- Evaluate available safety data using traditional and automated signal detection
- Assess signals
  - SMT owns decision for non-validated signals (i.e. «**Safety observations**»)
  - Validated signals are categorized into "**potential**" or "**identified**" **risks**
  - **Impact** of newly identified risks is determined (high vs. low):
    → Impact is assessed on the basis of its likelihood and consequences
- Escalate newly identified and important potential risks to MSRB or PSB
- Closely follow up on potential risks and consider additional data collection activities (e.g. studies, registries) to increase knowledge
- Trigger urgent safety measures or restrictions for newly identified high-impact risks
- Implement risk minimization measures by updating the Product Label, Investigators Brochure, Study Protocol, Risk Management Plan and discuss newly identified risks in DSURs and PSURs

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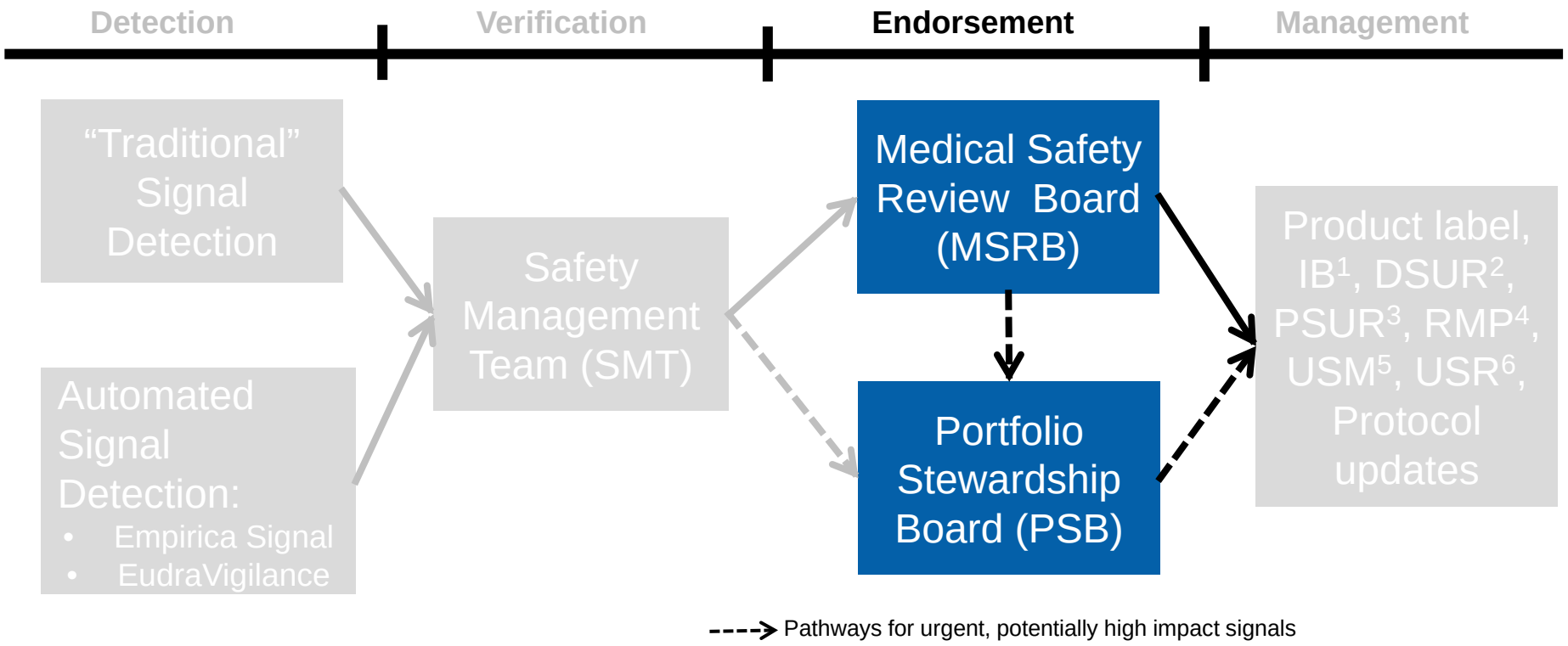
Signal endorsement and recommendations for action



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Medical Safety Review Board (MSRB)

Mission

- Meets weekly to ensure that safety risks vetted by the SMT are optimally managed from the formation of the SMT onwards throughout the drug life cycle

Composition

- **Mono-functional but multi-disciplinary** (e.g. Medical Safety, Risk Detection & Management, Quantitative Safety & Epidemiology, Mechanistic Safety, PK Sciences)

Reviews

- All new, potential safety signals verified by the Safety Management team
- Review of new risks for medicinal products in development
- Development Safety Profiling Plan (dSPP) version 1 and substantive revisions
- Risk Management Plan (RMP) version 1 and all substantive revisions
- Periodic Safety Update Report (PSUR) version 1

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Portfolio Stewardship Board (PSB)

Mission

- Ensure sound portfolio stewardship processes
- Oversee adequacy & compliance for safety processes and issues impacting the legal liability / reputation of the company and/or the benefit / risk of Novartis products/devices

Composition

- **Senior** Level Managers
- **Cross-functional** (e.g. Safety, Medical, Regulatory, Medical Affairs, Legal, Quality Assurance, Compliance, Technical Operations)

Underlying Principles

- Make decisions **independent** of commercial considerations

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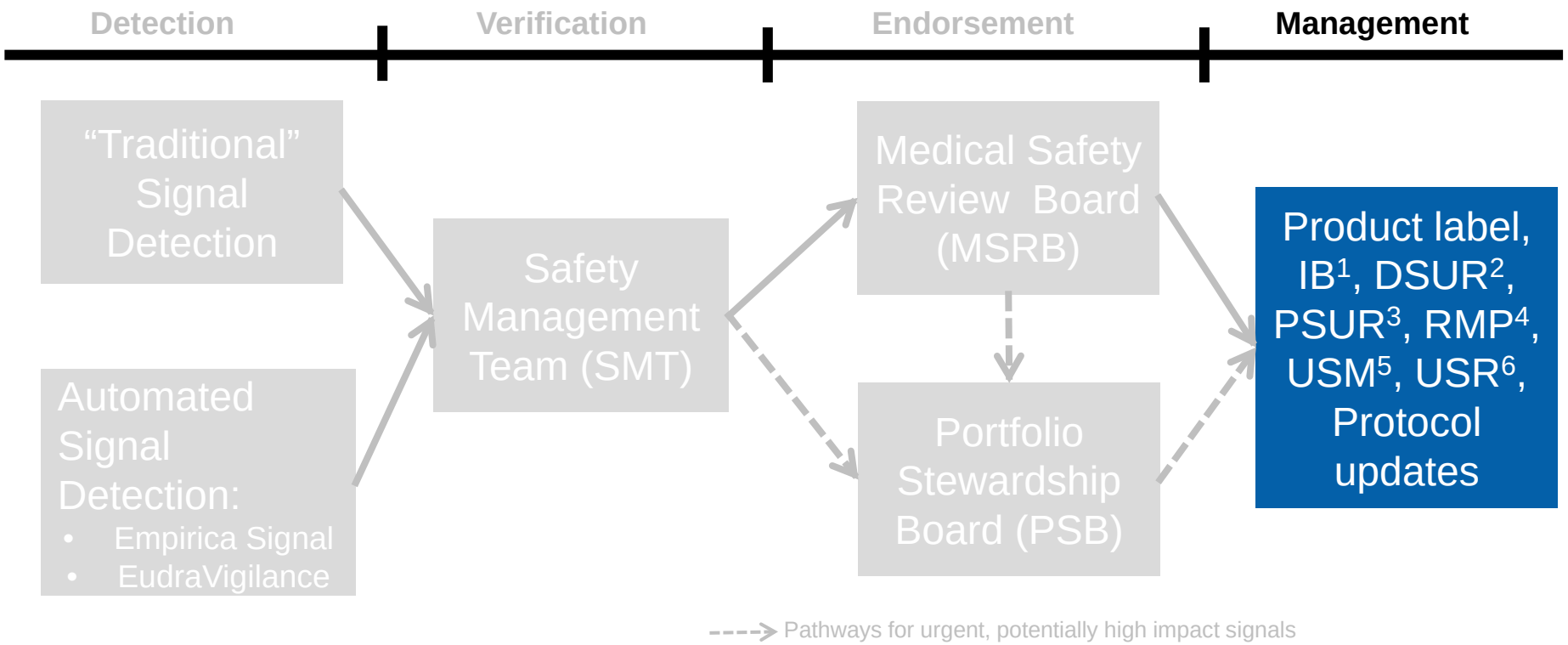
Risk management and mitigation



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Management of new risks

Overview

- **Expedited communication of high-impact risks:**
  - Urgent Safety Measures (**USM**) for development projects with ongoing studies
  - Urgent Safety Restrictions (**USR**) for marketed products
  - Dear Health Care Professional Letters (**DHCP** Letter)
- **Managing risks of development projects:**
  - Investigator Brochures (**IBs**) and Reference Safety Information (**RSI**) are updated to reflect newly identified risks
  - **Study protocols** and Informed Consent Forms **(ICFs)** are updated to reflect newly identified risks and risk minimization activities
  - Development Safety Update Reports (**DSURs**) present the new risks
  - Development Safety Profiling Plan (**dSPP** – internal document) is updated
- **Managing risks of approved products:**
  - The company Core Data Sheet (**CDS**) as well as **local labels** (e.g. **SmPC**) are updated to include new risks and mitigation activities
  - Risk Management Plans (**RMPs**) are updated to include new risks, risk minimization activities and appropriate measures of effectiveness
  - Periodic Safety Update Reports (**PSURs**) discuss the new risks
  - Safety Management and Reporting Tool (**SMaRT** – internal signal tracker) is updated

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Management of new risks

Systems used to manage risks

USM	• A procedure that can be put in place with immediate effect without needing to gain prior authorisation, to protect clinical trial participants from any immediate hazard
USR	• Urgent regulatory action triggered by the MAH*, a national regulatory authority or by the EC in the event of, or to prevent, a risk to human or animal health or to the environment
RMP	• Lists routine and additional pharmacovigilance activities for important risks, such as targeted studies, registries, educational material, targeted follow-ups checklists
IB/RSI	• Investigator Brochure and Reference Safety Information present known risks and give guidance to the investigator on how to prevent/mitigate risks to study participants
PSUR/ DSUR	• Periodic analysis of safety data to assess whether they change the known benefit-risk balance of compounds, with emphasis on identified and potential risks
dSPP	• Internal document that describes all identified and potential risks during the developmant phase – serves as a pre-decessor for the RMP
SMaRT	• Internal database where all safety signals are tracked throughout their life-cycle • Non-validated signals are also tracked to ensure full transparency

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Thank you

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