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BLOOMBERG SCHOOL
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Pharmacovigilance: Active Surveillance

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Definition of Active Surveillance

Postmarketing Surveillance

- ***Postmarketing surveillance*** is the “practice of monitoring the safety of a pharmaceutical or device after it has been released on the market”

- It includes:
  - Detection of safety signals
  - Testing hypothesis to generate evidence about the harm or safety of a product

Limitations of Spontaneous Reporting System

- Information submitted to the system is incomplete
- Denominators (number of individuals exposed to a drug) are unknown
  - Population-based (background) rates of an adverse event cannot be estimated from spontaneous reporting data
- Some adverse events are difficult to recognize
- Underreporting:
  - Reports could be as low as 10% of serious reactions
- There are reporting biases

Definition of Active Surveillance

- "Active surveillance, in contrast to passive surveillance, seeks to ascertain COMPLETELY the number of adverse events via a continuous, PRE-ORGANISED process"

Source: European Medicines Agency. Note for guidance on planning pharmacovigilance activities (CPMP/ICH/5716/03). Accessed on January 14, 2025, at https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use-topic-e-2-e-pharmacovigilance-planning-step-5_en.pdf

Types of Active Surveillance

- Use of **sentinel sites** for review of medical records or interviews of physicians (for complete capture of exposures and outcomes)
- Use of **drug event monitoring**
  - Exposed individuals identified in electronic sources and contacted for survey about outcomes
- **Registries** (drug exposure registries) in which observational studies can be nested
- **Big data** activities (e.g., use of distributed database)

Use of Sentinel Sites

Sentinel Sites

- Active surveillance can be achieved by reviewing medical records or interviewing patients and/or physicians in a sample of sentinel sites
- Goal: to capture complete and accurate data on reported adverse events from these sites
- The selected sites can provide information, such as data from specific patient subgroups, that would not be available in a passive spontaneous reporting system

Source: European Medicines Agency. Note for guidance on planning pharmacovigilance activities (CPMP/ICH/5716/03). Accessed on January 14, 2025, at https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use-topic-e-2-e-pharmacovigilance-planning-step-5_en.pdf

Example of Sentinel Sites: Vietnam

"Proposed is a pilot system for monitoring the safety and tolerability of antiretroviral therapy (ART) at sentinel sites in Vietnam through sentinel site active surveillance. It aims to develop, implement, and demonstrate the local feasibility of a practical and sustainable pharmacovigilance system that could later be scaled up to monitor the safety of antiretroviral medicine (ARV) regimens across Vietnam. It also has applicability for future active surveillance of other medicines, settings, and populations. The active surveillance activity, developed in consultation with stakeholders, proposes to systematically document and quantify the presence or absence of ARV-related adverse events and to determine risk factors at three sentinel sites in Vietnam. For this pilot activity, it is proposed that the active surveillance be initiated and evaluated at three outpatient ART health care facilities, two in Ho Chi Minh City (HCMC) and one in Hanoi. Systematically collecting information about medicines used in a defined population can help ensure that medicines have an acceptable safety profile and are used safely."

Source: Sentinel Site-Based Pilot Active Surveillance Pharmacovigilance in the Vietnam ART Program: Technical Assistance for Protocol Development. Accessed on January 14, 2025, at https://pdf.usaid.gov/pdf_docs/PNADU431.pdf

Similar Example in Karnataka, India

"The active surveillance system will be a multi-center, prospective observational cohort activity designed to evaluate the incidence and identify risk factors for adverse drug events among HIV-infected patients newly placed on antiretroviral therapy."

Source: Strengthening Pharmaceutical Services Program Final Report. Accessed on January 27, 2025, at: https://pdf.usaid.gov/pdf_docs/pdacy204.pdf

Use of Drug Event Monitoring and Registries

Drug Event Monitoring: Example

Patient-reported adverse events under asthma therapy: A community pharmacy–based survey

"Asthma patients aged 18–50 years were surveyed in 348 French pharmacies. Patients completed a questionnaire linked to computerized records of dispensed medications. Patients reported all AEs [adverse events] that they attributed to asthma therapy. The correlates of reporting 2+ AEs were identified. Almost 59% of the 1,351 patients (mean age: 37, 56% females) attributed AEs to asthma therapy, and 35% at least two. Most common AEs included tiredness (21.8%) and palpitations (21.1%). Poor asthma control and perception of asthma as a handicap were the major correlates of reporting 2+ AEs (odds ratio [OR]=2.5, 95% confidence interval [CI]=[1.7–3.7] and OR=1.9, 95% CI=[1.4–2.5])."

Source: Laforest, L., Van Ganse, E., Devouassoux, G., Osman, L. M., Bauguil, G., & Chamba, G. (2007). Patient-reported adverse events under asthma therapy: A community pharmacy-based survey. *Clinical Pharmacology and Therapeutics*, *82*(2), 167–172. https://doi.org/10.1038/sj.clpt.6100224

Registries

- Many exposure registries established for evaluation of adverse events associated with exposure to a medication
- Often involves active data collection
- Often sponsored by manufacturer at the requirement of the FDA
- Frequently used for evaluating exposures in pregnancy

Examples of Registries: Pregnancy Exposure Registries

Medicine	Medical condition	Registry contact information
COVID-19 vaccines	COVID-19	COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER) Website: https://c-viper.pregistry.com Phone: 1-800-616-3791
Abilify (aripiprazole)	Mental health disorders	National Pregnancy Registry for Atypical Antipsychotics Website: https://womensmentalhealth.org/research/pregnancyregistry Phone: 1-866-961-2388
Acitretin	Psoriasis	T.A.P.P. (Take Action to Prevent Pregnancy) Pregnancy Monitoring Program for acitretin PPD, Inc. Phone: 1-855-850-2138 Website: https://www.tevausa.com/our-products/tevagenerics/acitretin/

Source: List of Pregnancy Exposure Registries: From the FDA Office of Women's Health. Accessed on January 27, 2025, at: https://www.fda.gov/consumers/pregnancy-exposure-registries/list-pregnancy-exposure-registries

Use of Big Data

Newer Types of Active Surveillance

- Rely on use of large datasets
- Support data-mining activities
- Support hypothesis testing

Active Surveillance: Multiple Goals

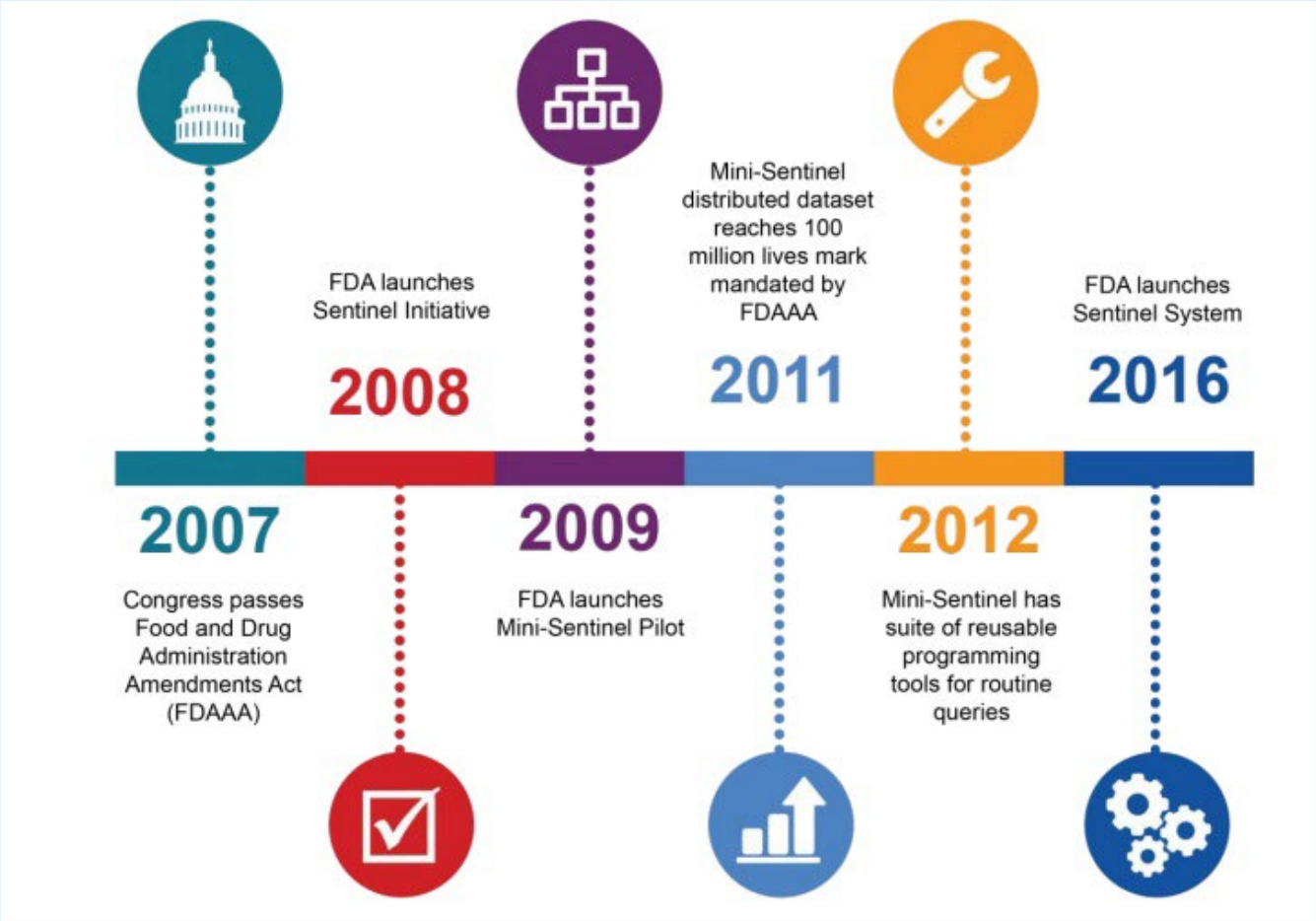
- Signal identification (can also be done with passive surveillance methods)
- Signal strengthening

US Food and Drug Administration (FDA)'s Sentinel Initiative

- FDA Amendments Act (FDAAA) of 2007 mandated active surveillance
- Sentinel Initiative launched in 2008, with the aim of facilitating the development of active surveillance methods related to "signal detection, strengthening, and validation"
- It gained even more attention with the 21st Century CURES Act, which calls for a framework for real-world evidence (RWE) for efficacy evaluation

Source: Sentinel Initiative. https://www.sentinelinitiative.org

History of the Sentinel Initiative



Source: Coyle, D. T., for the US FDA. (2017). Sentinel system overview [presentation]. Accessed on January 27, 2025, at: https://www.fda.gov/files/about%20fda/published/Sentinel-System-Overview---Presentation.pdf

Sentinel Uses Secondary Data

- Patient interaction with the US health care system generates data
  - **Administrative claims data:** collected for transactional recordkeeping, reimbursement
  - **Electronic health records data:** collected to document elements of clinical care and support physician decision-making

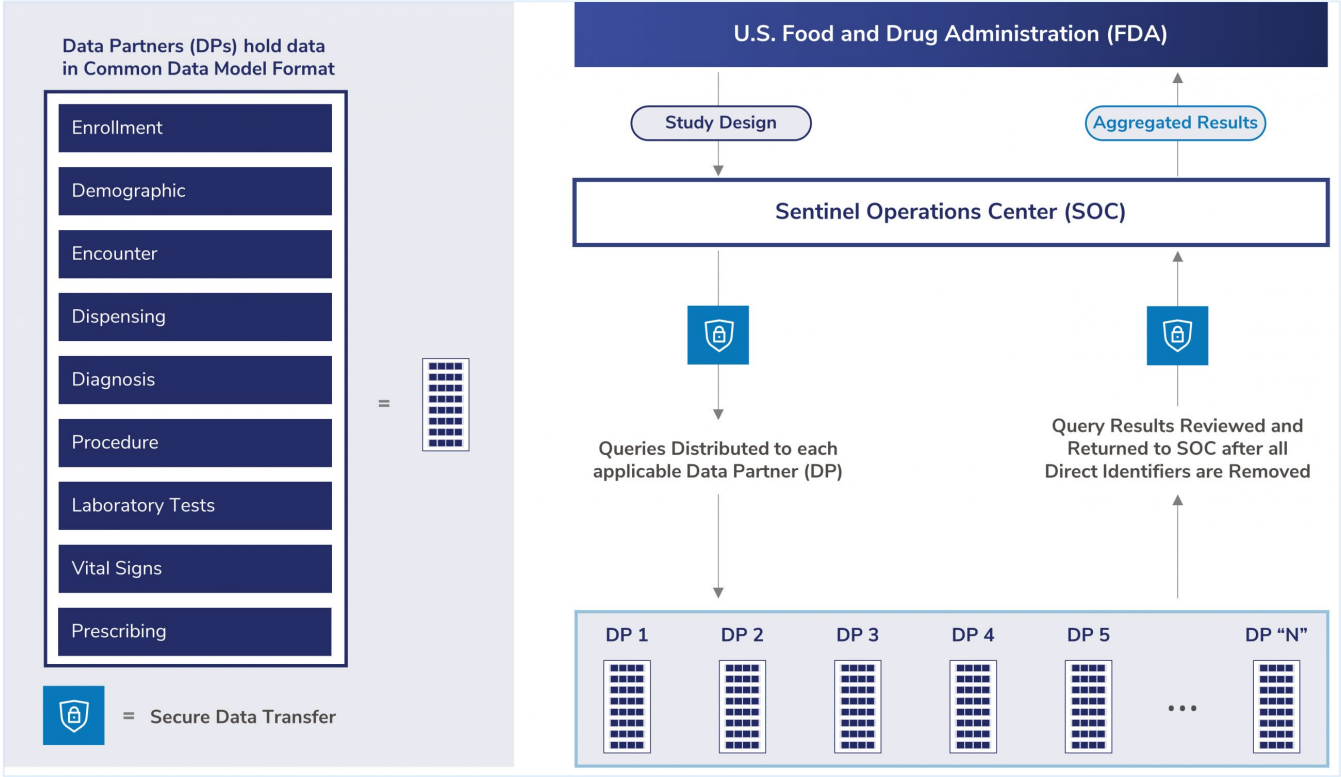
- Sentinel captures billions of encounters with multiple health care system partners

Common Data Model

- Sentinel uses a common data model as the basis for its analytic approach in order to work with multiple data partners
- Common data model approach requires the data partners to transform their data into a standardized format
- A common data “language” across multiple data partners allows for aggregation of large amounts of data

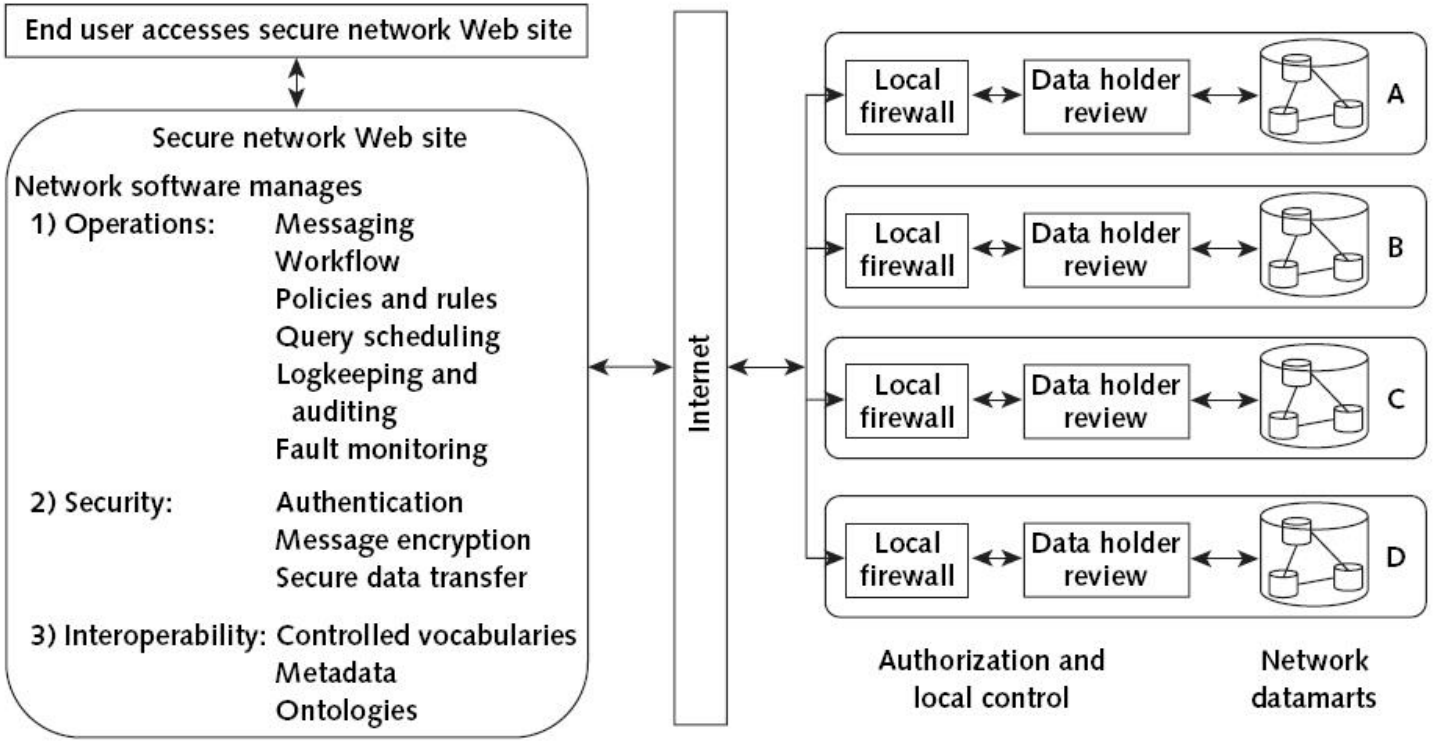
Distributed Database Structure

Principle task: ***signal refinement*** (assess evidence of association between an exposure and an outcome that are suspected to be related)



Source: Sentinel Initiative. How Sentinel Gets Its Data. Accessed on January 27, 2025, at: https://www.sentinelinitiative.org/about/how-sentinel-gets-its-data

Sentinel Structure



Source: Figure, "System operations in a distributed health network," in: Maro, J. C., Platt, R., Holmes, J. H., Strom, B. L., Hennessy, S., Lazarus, R., & Brown, J. S. (2009). Design of a national distributed health data network. *Annals of Internal Medicine*, *151*(5), 341–344. https://doi.org/10.7326/0003-4819-151-5-200909010-00139

Sentinel Distributed Database Statistics Summary, 2000–2024

- 1.3 billion person-years of data
- 129 million members currently accruing new data
- 24 billion unique medical encounters
- 22 billion pharmacy dispensings
- 73 million members with at least one laboratory test result

Source: Sentinel Initiative. Key Database Statistics. Accessed on January 27, 2025, at: https://www.sentinelinitiative.org/about/key-database-statistics

Active Risk Identification and Analysis (ARIA)

- ARIA is FDA's active post-market risk identification and analysis system, which comprises pre-defined, parameterized, reusable routine querying tools, combined with the electronic data in the Sentinel Common Data Model

Source: Sentinel Initiative. Drug Studies: Levels of ARIA Analyses. Accessed on January 27, 2025, at: https://www.sentinelinitiative.org/studies/drugs

An Example Drug Safety Study Using the Sentinel Initiative

- Question: Is risk of venous thromboembolism (VTE) higher with use of extended/continuous combined oral contraceptives (COCs) than with cyclic COCs?
  - **Population:** 210,691 continuous COC and 522,316 cyclic COC initiators
  - **VTE events:** 228 among continuous COC and 297 in cyclic COC
  - **Selected characteristics:** continuous COC users more likely to have:
    - Age ≥35 years, cardiovascular/metabolic conditions, gynecological conditions
  - **Propensity score–matched hazard ratio:** 1.32 (1.07–1.64)
  - **Adjusted absolute risk difference:** 0.27 per 1,000 persons
  - **Conclusion:** "… findings did not show strong evidence supporting a VTE risk difference …."

Source: Li, J., Panucci, G., Moeny, D., Liu, W., Maro, J. C., Toh, S., & Huang, T.-Y. (2018). Association of risk for venous thromboembolism with use of low-dose extended- and continuous-cycle combined oral contraceptives: A safety study using the Sentinel distributed database. *JAMA Internal Medicine*, *178*(11), 1482–1488. https://doi.org/10.1001/jamainternmed.2018.4251

Some of the Ongoing Sentinel Initiatives

"The Sentinel Innovation Center is a test bed to identify, develop, and evaluate innovative methods to study drug safety and effectiveness using real-world data."

- **Natural Language Processing (NLP):** Establish standards for NLP to identify complex health outcomes defined by multiple data elements
- **Advanced analytics:** Support maturation of advanced analytics, including machine learning, to improve evaluations of drug safety and effectiveness
- **Novel data sources:** Analyze utility of novel data sources, including patient-generated data
- **Data interoperability:** Explore harmonization of the Sentinel Common Data Model with other established and complementary models to expand the breadth of Sentinel System data
- **Emerging disruptive technologies:** Explore promising technologies through rapid prototyping or demonstration projects

Source: Sentinel Initiative. Sentinel Innovation Center. Accessed on March 13, 2025, at: https://www.sentinelinitiative.org/about/sentinel-structure/sentinel-innovation-center-ic

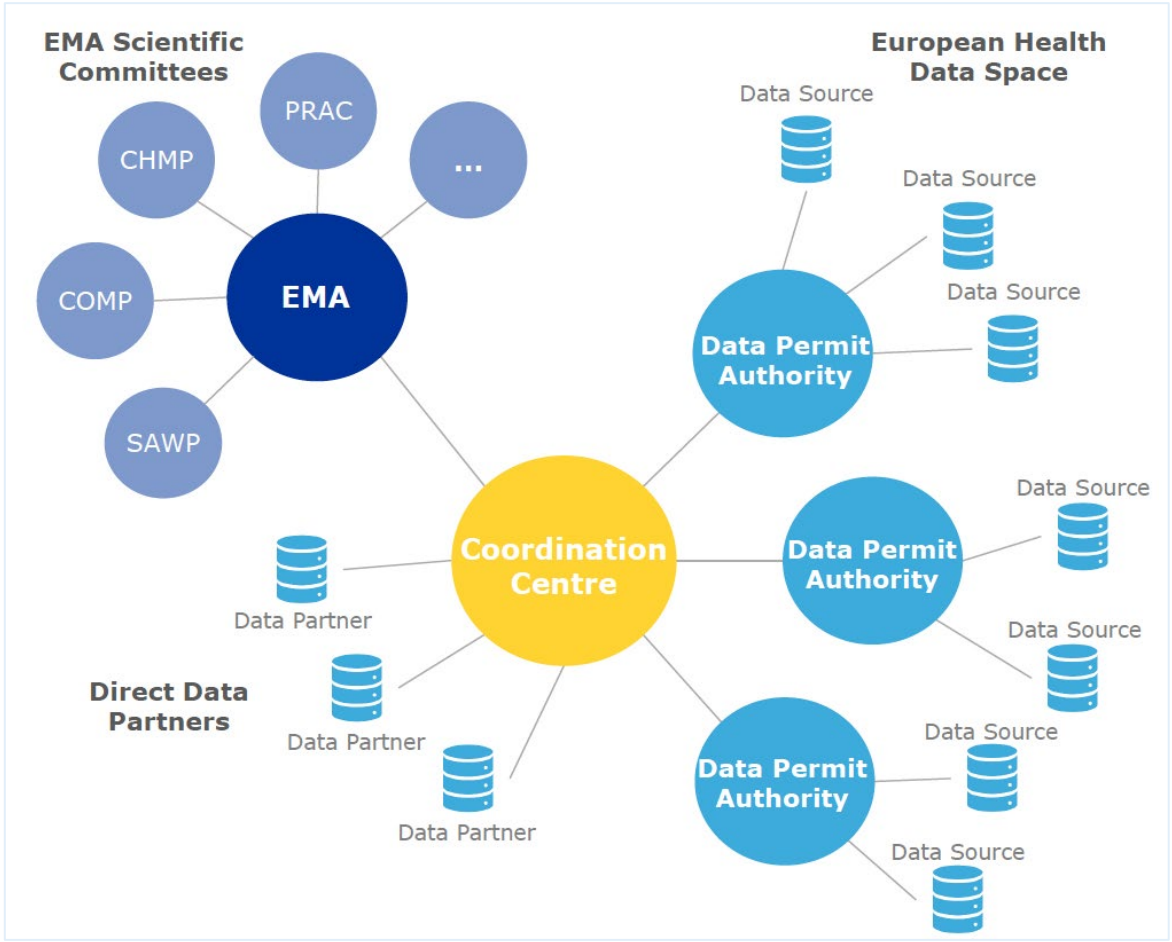
DARWIN EU—1

- The Data Analysis and Real-World Interrogation Network (DARWIN EU) is an initiative established in 2022 by the European Medicines Agency (EMA) and European Medicines Regulatory Network to create a data network for collecting and analyzing real-world data on the safety and effectiveness of medicines, including vaccines

- Similar to the Sentinel Initiative, DARWIN EU uses a distributed database with the Observational Medical Outcomes Partnership (OMOP) Common Data Model

Source: Data Analysis and Real World Interrogation Network (DARWIN EU®). https://darwin-eu.org/

DARWIN EU—2



Source: Darwin EU Network Requirements. Accessed on January 27, 2025, at: https://www.darwin-eu.org/index.php/data/network-requirements

International Active Surveillance System

Active Surveillance Systems That Use Big Data in the United States

Country	Program	Website
USA	FDA Sentinel Initiative	https://www.sentinelinitiative.org/
USA	FDA Biologics Effectiveness and Safety (BEST) Initiative	https://bestinitiative.org/
USA	CDC Vaccine Safety Datalink (VSD)	https://www.cdc.gov/vaccine-safety-systems/vsd/index.html

Active Surveillance Systems That Use Big Data Worldwide

Country	Program	Website or related publication
EU	DARWIN-EU	https://www.ema.europa.eu/en/about-us/how-we-work/big-data/real-world-evidence/data-analysis-real-world-interrogation-network-darwin-eu
Canada	Canadian Network for Observational Drug Effect Studies (CNODES)	https://www.cnodes.ca/
Canada	Canadian Adverse Events Following Immunization Surveillance System (CAEFISS)	https://www.canada.ca/en/public-health/services/immunization/canadian-adverse-events-following-immunization-surveillance-system-caefiss.html
UK	Medicines & Healthcare products Regulatory Agency (MHRA)—The Vigilance and Risk Management of Medicines Division	https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency
Australasia	Asian Pharmacoepidemiology Network (AsPEN)	https://www.aspensig.asia/
Japan	Medical information database network (MID-NET)	Yamaguchi, M., et al. (2019). *Pharmacoepidemiology and Drug Safety*, *28*(10), 1395–1404. https://doi.org/10.1002/pds.4879
China	National Adverse Drug Reaction Monitoring Sentinel Alliance Program	Zhao, Y., et al. (2018). *International Journal of Clinical Pharmacy*, *40*(4), 823–831. https://doi.org/10.1007/s11096-018-0693-x

Summary

- Active surveillance, in contrast to passive surveillance, seeks to ascertain **completely** the number of adverse events via a continuous, **pre-organized** process

- In this system, investigators know the denominator and can estimate the background rate of an adverse event associated with a medication

- Four types of active surveillance:
  1. Use of sentinel sites
  2. Drug monitoring program
  3. Registries
  4. Use of big data

- FDA Sentinel Initiative launched in 2008, with the aim of facilitating the development of active surveillance methods related to “signal detection, strengthening, and validation”

- Active surveillance systems exist worldwide