All information regarding future IHI Call topics is indicative and subject to change. Final information about future IHI Calls will be communicated after approval by the IHI Governing Board.

Topic 3: AI-powered signal detection in pharmacovigilance

Expected outcomes

Industry, regulators, researchers and other stakeholders have access to evidence-based and practical guidance, with aligned perspectives of public and private stakeholders, on the use of artificial intelligence (AI) for signal detection and other pharmacovigilance (PV) applications to ensure patient safety.

Patients and citizens will benefit from earlier and more accurate signal detection, which will lead to earlier risk communication and more effective measures to manage the risks.

More specifically the action under this topic must contribute to all of the following outcomes (which can be applied to various therapeutic areas irrespective of the size and composition of the safety database and to products under development as well as those in post-marketing setup):

- AI-powered algorithms and methods for faster and more accurate signal detection;
- a comprehensive list of data sources where AI methods could be used for improved signal detection, including a set of recommendations, along with principles to be followed to support a suitable common data model for simultaneous analyses of a wide range of different data sources (including clinical trials and post-marketing surveillance data) for the same purpose;
- AI-powered algorithms and methods for highly accurate risk prediction to help identify potential risks in the future before they escalate into significant public health issues and enable proactive measures to mitigate risks;
- recommendations, including practical considerations for implementing AI-powered signal detection and risk prediction systems in real-world scenarios, to enable effective and trusted use of AI;
- tools and templates for practical implementation of AI – power signal detection and risk predictions by the public and private stakeholders;
- training and user guides and other education materials on the implementation of the recommendations and the use of AI.

Central to the delivery of these outcomes are transparency, trustworthiness, and adherence to the ethical and legal principles of the use of patient-level data and any proprietary information.

Scope

Spontaneous reporting systems (SRSs) have been essential for signal detection in pharmacovigilance but suffer from low accuracy and delays, impacting patient safety. More recently, electronic health records (EHRs) have also been used for signal detection[1], but the performance needs to be improved [1]. A safety signal is information on a new or known adverse event that may be caused by a medicine

[1] Signal Identification Methods in the Sentinel System

and requires further investigation[2]. Signal detection is the identification of potential exposure-outcome relationships that warrant further consideration.

AI offers a promising solution by improving the efficiency, accuracy, and timeliness of signal detection using diverse and untapped data sources to allow for enhanced and timely benefit-risk profile evaluation. Recent regulatory developments include the FDA's January 2025 guidance on AI for decision-making (FDA Guidance AI), which provides recommendations for using AI in regulatory decision-making about drug safety and effectiveness. Additionally, the EMA's September 2024 reflection paper (EMA- Reflection paper on AI) discusses AI's role throughout the lifecycle of medicinal products, from drug discovery to post-authorisation.

Advances in digital technology and computer science, such as generative AI, machine learning, and predictive analytics, have the potential to enable faster and more accurate analysis of both traditional and emerging data sources, which will improve patient safety, provision of healthcare, and public health. There are different PV areas where AI could potentially be applied, including individual case safety report (ICSR) management, periodic reports, signal detection, and risk management. The scope of this topic focuses on the use of AI for signal detection and risk prediction. It also covers opportunities that may not be 'signal detection' per se but rather augmentations/support beyond signal detection for instance with the expanded use of data and AI-powered methods, including characterisation of cases that can provide context for interpreting an exposure-outcome relationship.

The use of AI for ICSR management and processing as well as periodic reports are out of the scope of this topic.

To fulfill this aim, the action funded under this topic should:

1. Evaluate, select, optimise and test AI algorithms using disparate data sources for signal detection. This implies:
   - carrying out a review of existing literature, including results from previous initiatives. and practical applications. This will help to understand the strengths and limitations of different approaches and identify a collection of systems, AI methods, and tools that have been tested on various data sources;
   - selecting the most effective algorithms for signal detection based on this review;
   - pilot testing the algorithms to evaluate their performance using a series of use cases against different business scenarios from different stakeholders' perspectives. Performance metrics include accuracy, reliability/repeatability, and trustworthiness. The criteria of the use case studies will be developed at an early stage of the project when promising algorithms and tools have been identified;
   - optimising AI algorithms to perform signal detection at the level of a medical concept or syndrome, with emphasis on transparency requirements, including model interpretability, data provenance, and traceability of AI decision-making processes.
2. Evaluate diverse data sources to be considered within a cohesive pharmacovigilance network for the purpose of signal detection. This implies:
   - identifying data sources and reference datasets needed to pilot test the algorithms. This will include EHRs (medical records, claims, registries) as one of the main data sources in this project and other data sources such as spontaneous reporting systems (EudraVigilance, FDA Adverse Events Reporting System FAERS and WHO Vigibase), social media and genomics;
   - evaluating these data sources addressing their overall quality, how fit they are for purpose, current limitations and future opportunities, such as electronic health records, social media

[2] Signal management | European Medicines Agency (EMA)

platforms, and others. This includes evaluating them individually or simultaneously to ensure a holistic view of drug safety, enhancing the analysis and monitoring of adverse drug reactions for a more thorough understanding of drug safety;

- developing a set of recommendations that could be utilised for simultaneous analyses of different data sources, along with the principles to be followed to support a common data model for evaluating different data sources for the same purpose.

3. Evaluate and develop predictive models to identify risks in the future (risk prediction).
    - based on the results from signal detection, develop predictive models using different data sources that may help identify potential risks in the future before they escalate into significant public health issues. These models would use historical data and advanced analytics to forecast potential risks, potentially enabling proactive measures to mitigate risks.
4. Develop a recommendations document for implementing AI-powered signal detection and risk prediction systems in real-world scenarios
    - using the results from the pilot tests, design a recommendations document which will serve as a reference for implementing AI-powered signal detection and risk prediction systems in real-world scenarios. The recommendations will include a set of principles and practical considerations to enable effective, explainable, and trusted use of AI and will include ethical, legal, and governance considerations for the sharing and use of real-world data and AI-algorithms;
    - engage with the European Medicines Agency (EMA) to seek endorsement of the recommendations document via the “Qualification Procedure”.
5. Develop recommendations for human-in-the-loop (HITL) and human-on-the-loop (HOTL) AI in pharmacovigilance signal detection for optimal performance and oversight.
6. Develop templates and tools for practical implementation, including integration into existing PV systems of AI – power signal detection and risk prediction models by different stakeholders.
7. Develop training plans and education materials to disseminate the recommendations widely to the stakeholder community and develop a strategy for uptake.

For all these activities, applicants are expected to adhere to ethical and legal principles. For instance for trustworthy AI, human oversight and verifications will follow regulatory frameworks such as the Assessment List for Trustworthy Artificial Intelligence (ALTAI).

Applicants are expected to develop a regulatory strategy and interaction plan for evidence generation to support the regulatory qualification of the methodology as relevant and engage with regulators in a timely manner (e.g. national competent authorities, EMA Innovation Task Force, qualification advice).

Applicants are also expected to foster proactive and early involvement of regional healthcare systems and health authorities in all stages of the discussion and decision-making processes.

Expected impacts

The action under this topic is expected to achieve the following impacts:

- enhanced drug safety by improving the speed and accuracy of identifying adverse drug reactions (signal detection);
- proactive risk management by improving risk assessment and prediction, scalability in monitoring, and fostering collaboration among stakeholders;
- improved patient safety through an earlier and more effective risk management plan, risk communication, and risk mitigation;

- faster and more informed decision-making through AI-driven insights;
- increased efficiency through rapid processing of vast amounts of data at a much faster rate compared to traditional methods;
- streamlined processing by automating routine pharmacovigilance tasks, thereby reducing the manual workload for healthcare professionals, and the operational costs associated with these activities;
- support for future policies and the shaping of regulations through evidence generated on the use of AI in signal detection and pharmacovigilance to improve patient safety;
- increased consistency in approaches used by industry, academia and regulators.

The action will also support the EU political priority to boost European competitiveness and contribute to a number of European policies/initiatives, which include European policies and regulations on AI for signal detection, the Regulation on the European Health Data Space (EHDS)[3] through recommendations of data space for pharmacovigilance activities, the EU Artificial Intelligence Act[4] and the European Health Emergency Preparedness and Response Authority (HERA) through earlier risk communication and mitigation.

Why the expected outcomes can only be achieved by an IHI JU action

The successful integration of diverse data sources and the development of advanced AI algorithms necessitate a collaborative effort. This multi-disciplinary collaboration brings together expertise from various fields, including data science, pharmacovigilance, regulatory affairs, and clinical research. It is crucial to unite public and private sectors, along with different biopharma industries, to address these challenges effectively. The Innovative Health Initiative Joint Undertaking (IHI JU) plays a crucial role in facilitating this collaboration by providing a platform where experts from different disciplines can work together towards common goals.

Regulatory science and oversight are at the heart of pharmacovigilance and therefore the active involvement of regulators in this collaborative partnership is needed to foster shared confidence in AI tools, regardless of who is using them.

A public-private partnership is the ideal framework to bring all stakeholders, which includes patients, academics, industry, regulators to align on overarching principles to minimise risks.

Large-scale projects often require significant resources and infrastructure that individual organisations might find challenging to provide on their own. By bringing together public and private sectors, the IHI setting addresses this challenge by offering the necessary support, including funding, technological infrastructure, and access to a network of experts. This support enables the successful execution of ambitious projects that have the potential to make a substantial impact on the field.

Pre-identified industry consortium

The pre-identified industry consortium that will contribute to this cross-sectoral IHI JU project is composed of the following medical technology industry beneficiaries (‘constituent or affiliated entities of private members’):

- AbbVie
- Amgen
- Astellas

[3] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=OJ:L_202500327
[4] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32024R1689

- AstraZeneca
- Biogen
- Bristol Myers Squibb
- GSK
- Johnson & Johnson
- Merck KGaA
- MSD
- Novartis
- Novo Nordisk
- Pfizer
- Roche
- Sanofi (Lead)
- Takeda
- UCB

In the spirit of partnership, and to reflect how IHI JU two-stage call topics are built upon identified scientific priorities agreed together with a number of proposing industry beneficiaries (i.e. beneficiaries who are constituent or affiliated entities of a private member of IHI JU), it is envisaged that IHI JU proposals and actions may allocate a leading role within the consortium to an industry beneficiary. Within an applicant consortium discussing the full proposal to be submitted for stage 2, it is expected that one of the industry beneficiaries may become the project leader. Therefore, to facilitate the formation of the final consortium, all beneficiaries, affiliated entities, and associated partners are encouraged to discuss the weighting of responsibilities and priorities regarding such leadership roles. Until the role is formalised by execution of the Grant Agreement, one of the proposing industry beneficiaries shall, as project leader, facilitate an efficient drafting and negotiation of project content and required agreements.

Indicative budget

- The maximum financial contribution from the IHI JU is up to EUR 8 906 000.
- The indicative in-kind contribution from industry beneficiaries is EUR 11 418 645.

Due to the global nature of the participating industry partners, it is anticipated that some elements of the contributions will be in-kind contributions to operational activities (IKOP) from those countries that are neither part of the EU nor associated to the Horizon Europe programme.

The indicative in-kind contribution from industry beneficiaries may include in-kind contributions to additional activities (IKAA).

Indicative duration of the action

The indicative duration of the action is 60 months.

This duration is indicative only. At the second stage, the consortium selected at the first stage and the predefined industry consortium may jointly agree on a different duration when submitting the full proposal.

Contribution of the pre-identified industry consortium

The pre-identified industry consortium expects to contribute to the IHI JU project by providing the following expertise and assets:

- AI and machine learning specialists:
  - data scientists to develop and implement AI, machine learning, and other AI-powered models for signal detection;
  - natural language processing (NLP) experts for processing and analysing unstructured data from various sources like medical literature and social media.
- Pharmacovigilance experts:
  - pharmacologists to understand drug safety and adverse event reporting;
  - regulatory experts to ensure compliance with regulatory standards and guidelines.
- Ethics and data protection specialists
- Healthcare data analysts, real-world data/real-world evidence experts:
  - epidemiologists for analyses of trends and patterns in adverse event data and for validation of signals;
  - biostatisticians for statistical analysis and validation of signals.
- IT and data management professionals:
  - database administrators: to manage large datasets and ensure data integrity;
  - software engineers: to develop and maintain the infrastructure for AI applications.

Applicant consortium

The first stage applicant consortium is expected, in the short proposal, to address the scope and deliver on the expected outcomes of the topic, taking into account the expected contribution from the pre-identified industry consortium and, where available, building on existing structures.

This may require mobilising the following expertise:

- pharmacovigilance, epidemiology, biostatistics;
- data science, AI;
- risk modelling, risk assessment and risk management;
- data privacy and protection, ethics;
- experience in engaging with patients;
- regulatory and compliance Framework Standard Operating Procedures (SOPs): expertise for AI model validation and monitoring;
- project management experience for large multi-stakeholder European public-private partnerships.

Furthermore, the applicant consortium is expected to provide the below resources:

Technological infrastructure:

- high-performance computing for processing large volumes of data;
- data storage solutions to securely store and manage data from various sources.

Access in a GDPR-compliant (General Data Protection Regulation) manner to data sources:

- electronic Health Records (EHRs): comprehensive patient data for analysis;

- spontaneous reporting systems: voluntary reports of adverse drug reactions;
- medical literature;
- other emerging data sources arising from new advancements in digital technology and computer science (such as social media, laboratory outputs, radiology data, genomics): to be used for exploratory purposes and additional insights as well as other datasources currently in use, including chemometric, biologic;
- all project members need to have access in a GDPR-compliant manner to these data sources;
- data must comply with GDPR and informed patient consent regulations.

The applicant consortium is expected to enable effective collaboration with regulatory authorities, national competent authorities, and may consider, for instance, engaging them as consortium partners, or in an advisory capacity.

At the second stage, the applicant consortium selected at the first stage and the pre-identified industry consortium will form the full consortium. Considering the role of the European Medicines Agency (EMA) in coordinating the European Union (EU) pharmacovigilance system and operating services and processes to support pharmacovigilance in the EU, EMA is prepared to join the applicant consortium selected at the first stage along with the pre-identified industry consortium (the full consortium). EMA's provisions include substantial and unique data access and expertise, as well as sharing experience from ongoing activities with national competent authorities exploring AI use cases in pharmacovigilance.

The full consortium will develop the full proposal in partnership, including the overall structure of the work plan and the work packages, based upon the short proposal selected at the first stage.

Dissemination and exploitation obligations

The specific obligations described in the conditions of the calls and call management rules under 'Specific conditions on availability, accessibility and affordability' do not apply.

Eligibility for funding

The specific conditions whereby applicants may receive funding in Call 11 will be published together with the Call 11 topic text.

References

[1] Taylor LG, Kürzinger ML, Hermans R, Enshaeifar S, Dwan B, Chhikara P, Li X, Thummisetti S, Colas S, Duverne M, Juhaeri J. Considerations for practical use of tree-based scan statistics for signal detection using electronic healthcare data: a case study with insulin glargine. Expert Opin Drug Saf. 2024 Aug 23:1-11. doi: 10.1080/14740338.2024.2393274. Epub ahead of print. PMID: 39162331.

Glossary

Acronym	Meaning
AI	Artificial intelligence
EHDS	European Health Data Space
EHRs	Electronic Health Records
EMA	European Medicines Agency
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
GDPR	General Data Protection Regulation
HERA	European Health Emergency Preparedness and Response Authority
HITL	Human in the Loop
IHI JU	Innovative Health Initiative Joint Undertaking
IKAA	in-kind contributions to additional activities
IKOP	in-kind contributions to operational activities
NLP	Natural language processing
PV	Pharmacovigilance
SOPs	Standard Operating Procedures
SRSs	Spontaneous reporting systems