PRECISEU

DELIVERABLE 4.2

Interoperability Framework

BSC, ART-ER, CLUST-ER HEALTH & FORTH

Deliverable's Due Date: 30/06/2026

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EU Project officer	Christina Nanou
Project coordinator	Montse Daban (Biocat)
Project manager	María Cejas (Biocat)

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*Legend = **R –** Report // **DEM –** Demonstrator, pilot, prototype, plan designs // **DEC –** Websites, patents filing, press & media actions, videos, etc. // **DMP –** Data management plan // **OTHER –** Software, technical diagram, algorithms, models, etc.	

Table 2. Deliverable information

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Task 4.2 CONSORTIUM PARTNERS

	Name of the Entity	Acronym	Role	Country	ORG Type
1	BARCELONA SUPERCOMPUTING CENTER CENTRO NACIONAL DE SUPERCOMPUTACIÓN	BSC-CNS	B	Spain	
2	ART-ER-SOCIETA CONSORTILE PER AZIONI[1]	ART-ER	B	Italy	
3	CLUST ER INDUSTRIE DELLA SALUTE E DEL BENESSERE	CLUST-ER HEALTH	B	Italy	
4	IDRYMA TECHNOLOGIAS KAI EREVNAS	FORTH	B	Greece	

***Legend** = Role in the Project: **C** – Coordinator // **B** – Beneficiary // **AP** – Associated Partner // Organization Type: **RTD** – Research and Technological Development// **PHI** – Public Health Institution // **Hosp –** Hospital // **SME** – Small and medium-sized enterprises. // **LC** – Large Company // **NGO** – Non-Governmental Org.

1. ART-ER has contributed as PRECISEU beneficiary under D4.2, updating the contributors list appearing in the Grant Agreement

Table 3. Task 4.2 PRECISEU consortium

CONSORTIUM PARTNERS

	Name of the Entity	Acronym	Role	Country
1	Biocat LA FUNDACIO BIOREGIO DE CATALUNYA	Biocat	COO	ES
2	DEPARTAMENT DE SALUT- GENERALITAT DE CATALUNYA	SALUT	BEN	ES
3	BARCELONA SUPERCOMPUTING CENTER CENTRO NACIONAL DE SUPERCOMPUTACION	BSC-CNS	BEN	ES
4	BIORN CLUSTER MANAGEMENT GMBH	BIORN	BEN	DE
5	BIOPRO BADEN-WUERTTEMBERG GMBH	BIOPRO	BEN	DE
6	AGENTIA PENTRU DEZVOLTARE REGIONALA NORD-EST	NE RDA	BEN	RO
7	ASOCIATIA DIGITAL INNOVATION ZONE ZONA DE INOVARE DIGITALA	DIZNE	BEN	RO
8	CLUSTERUL REGIONAL INOVATIV DE IMAGISTICA MOLECULARA SI STRUCTURALA NORD-EST (IMAGO-MOL)	IMAGO-MOL	BEN	RO
9	BIOTEHNOLOGICHEN I ZDRAVEN KLASTER	HLSCB	BEN	BG
10	STOLICHNA OBSHTINSKA AGENTSIA ZA PRIVATIZATSIA I INVESTITSII	SIA	BEN	BG
11	CLUST ER INDUSTRIE DELLA SALUTE E DEL BENESSERE	CLUST-ER HEALTH	BEN	IT
12	REGIONE EMILIA ROMAGNA	RER	BEN	IT

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	Name of the Entity	Acronym	Role	Country
13	ART-ER-SOCIETA CONSORTILE PER AZIONI	ART-ER	BEN	IT
14	VLAAMSE GEWEST	EWI	BEN	BE
15	MEDVIA	MEDVIA	BEN	BE
16	VIESOJI ISTAIGA INOVACIJU AGENTURA	IA LITHUANIA	BEN	LT
17	BRG, BUSINESS REGION GOTEBORG AB	BRG	BEN	SE
18	EATRIS ERIC	EATRIS	BEN	NL
19	PLATAFORMA DE ORGANIZACIONES DE PACIENTES	POP	BEN	ES
20	AGENCIA PER A LA COMPETITIVITAT DE LA EMPRESA	ACCIO	BEN	ES
21	IDRYMA TECHNOLOGIAS KAI EREVNAS	FORTH-ICS	BEN	EL
22	REGION OF CRETE	CRETE	BEN	EL
23	SAHLGRENSKA SCIENCE PARK AB	SSP	BEN	SE
24	RIVNE INTERREGIONAL MEDICAL CLUSTER	RIVNE	BEN	UA
25	ASTRAZENECA FARMACEUTICA SPAIN S.A.	ASTRA ZENECA	BEN	ES
26	AGENCIA DE TRANSFORMACIÓN DIGITAL DE CASTILLA – LA MANCHA	ATD	BEN	ES
27	LAZIO INNOVA	LI	BEN	IT
28	NATIONAL INSTITUTE FOR BIOPROCESSING RESEARCH AND TRAINING	NIBRT	BEN	IE

Table 4. Consortium partners

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WORK PACKAGES AND LEADERS

Work Packages Name		WP Leader
WP 1	Project Management and Coordination	Biocat
WP 2	Communication and Dissemination	NE RDA
WP 3	Interregional Collaboration and Partnership Bridging	IA Lithuania
WP 4	Use of Health Data	ART-ER
WP 5	Multistakeholder infrastructure to enable access to ATMP on large scale	BIO PRO
WP 6	Market and Patient Access	SSP
WP 7	Training and Cultural Change	HLSCB
WP 8	Adoption of PM innovations in the HealthCare System	SALUT
WP 9	Innovation Support Program	Biocat

Table 5. PRECISEU'S Work Packages and Leaders

How to quote this document
Aída Moure, Laura Portell/ BSC; Clémence Foltz/ Clust-ER Health; Apostolos Dimitriadis/FORTH (2026).
PRECISEU D4.2 Interoperability Framework, *Barcelona Supercomputing Center (BSC)*

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LIST OF ACRONYMS AND ABBREVIATIONS

Abbreviation	Definition/Description
(N)HIS	(National) Health Information System
ABAC	Attribute-Based Access Control
ACN	National Cybersecurity Agency (Italy)
AEPD	Agencia Española de Protección de Datos (Spanish Data Protection Agency)
AES	Advanced Encryption Standard
AGENAS	AGEnzia NAzionale per i servizi Sanitari (Italian national body for monitoring and improving NHS)
AI	Artificial Intelligence
API	Application Programming Interface
ART-ER	ART-ER (Italy) Società Consortile per Azioni
ATC	Anatomical Therapeutic Chemical Classification System
ATMP	Advanced therapy medicinal products
BIOCAT	Fundació BioRegió de Catalunya
BIOPRO	BIOPRO Baden-Württemberg GmbH
BPPC	Basic Patient Privacy Consents
BSC	Barcelona Supercomputing Center
CAMSS	Common Assessment Method for Standards and Specifications
CC	Central Component
CCDR	Centralised Clinical Data Repository
CDISC	Clinical Data Interchange Standards Consortium
CEAS	Electronic Health Insurance Card System (Romania)
CEN	European Committee for Standardisation
Cl@ve	Electronic Identification System (Spain)
CLUST-ER	Clust-ER Health (Italy)
CNR-IRPPS	Istituto di Ricerca sulla Popolazione e le Politiche Sociali (Italy)
CPD	Continuing Professional Development
CPMS	Clinical Patient Management System
CSA	CyberSecurity Act
CSV	Comma-separated values
D4.2	Deliverable 4.2
DCAT-AP	Data Catalog Vocabulary — Application Profile
DES	Digital Electronic Record (Romania)
DGA	Data Governance Act
DGIA	Dutch GDPR Implementation Act
DICOM	Digital Imaging and Communications in Medicine
DLC	Data Life Cycle
DNIe	Documento Nacional de Identidad electrónico (Spain)
DoA	Description of Action
DOI	Digital Object Identifier
DPA	Data Protection Authority
DPIA	Data Protection Impact Assessment
DPO	Data Protection Officer
DRG	Diagnosis Related Group
EATRIS	European infrastructure for translational medicine
EC	European Commission
EDPS	European Data Protection Supervisor
EDS	Ecosistema Dati Nazionali (Italy)

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Abbreviation	Definition/Description
EEHRxF	European Electronic Health Record Exchange Format
EHDS	European Health Data Space
EHR	Electronic Health Record
eID	Electronic Identification
eIDAS	electronic Identification, Authentication and trust Service
EIF	European Interoperability Framework
EISMEA	European Innovation Council and SMEs Executive Agency
ELIXIR	Research infrastructure for life-science data
ELSI	Ethical, Legal, Social Issues
EMR	Electronic Medical Record
ENSALUD	National Digital Health and eHealth Initiatives (Spain)
ePA	Electronic Patient Record (Germany)
ERN	European Reference Network
ESHIA	Alliance for health standard
ESPBI IS	State Electronic Health Services and Cooperation Infrastructure Information System
EU	European Union
EUCAIM	European Federation for Cancer Images
FAIR	Findable, Accessible, Interoperable, Reusable
FHIR	Fast Healthcare Interoperability Resources
FORTH	Foundation for Research and Technology – Hellas
FPS Health	Federal Public Service Health, Food Chain Safety, and Environment (Belgium)
FSE	Fascicolo Sanitario Elettronico (Italian national EHR)
GA4GH AAI	Global Alliance for Genomics and Health Authentication and Authorisation Infrastructure
GARR	A national research and education network
GDI	Genomic Data Infrastructure
GDPR	General Data Protection Regulation
genomDE	German National Genomics Initiative
GP	General Practitioner
HDA	Health Data Agency
HDAB	Health Data Access Body/Bodies
HIE	Health Information Exchange
HL7	Health Level 7
HPC	High Performance Computing
ICD-10	International Classification of Diseases, 10th Revision
ICD-11	International Classification of Diseases, 11th Revision
ICPC	International Classification of Primary Care
IDIKA	Greek e-Government Center for Social Security
IHE	Integrating the Healthcare Enterprise
INI	National Infrastructure for Interoperability (Italy)
IPR	Intellectual Property Rights
IPR-AWP	Internal Progress Report- Annual Work Plan
ISO/IEC	International Standards Organisation / International Electrotechnical Commission
IT	Information Technology
IVDR	In Vitro Diagnostic Regulation
JIP	Joint Interregional Projects
LEPIDA	Regional IT company (Italy)
LOINC	Logical Observation Identifiers Names and Codes
LOPDGDD	Organic Law on Data Protection and Guarantee of Digital Rights
MDR	Medical Device Regulation
MIE	Medical Informatics Europe

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Abbreviation	Definition/Description
MII	Medical Informatics Initiative (Germany)
MIS	Management Information Systems
MLLP	Minimal Lower Layer Protocol
MoH	Ministry of Health
MPI	Master Patient Index
MQTT	Message Queuing Telemetry Transport
MTA	Material Transfer Agreements
Nanodiag BW	Innovation Cluster and Research Network (Germany)
NCPeH-NL	National Contact Point for eHealth Netherlands
NextGenEU	European Union's Large-scale Economic Recovery Plan
NHIF	National Health Insurance Fund
NHIS	National Health Information System
NHS	National Health Service
NIHDI	National Institute for Health and Disability Insurance (Belgium)
NIS2	Network and Information Security Directive 2
NLM	Natural Language Model
NLP	Natural Language Processing
NSIS	Nuovo Sistema Informativo Sanitario (the national backbone of Italy's health Information System)
OAI-PMH	Open Archives Initiative Protocol for Metadata Harvesting
OAuth 2.0	Open Authorization Standard
OHDSI	Observational Health Data Sciences and Informatics
OMOP CDM	Observational Medical Outcomes Partnership
ONDS	National Health Data Observatory (Romania)
ORCiD	Open Researcher and Contributor ID
PACS	Picture Archiving and Comunication System
PDPA	Personal Data Protection Act
PERTE	Strategic Project for Economic Recovery and Transformation (Spain)
PGHD	Patient Generated Health Data
PIAS	Integrated Health Insurance Platform
PIX/PDQ	Patient Identity and Demographics Query (IHE profile)
PRECISEU	PeRsonalised medicine Empowerment Connecting Innovation ecoSystems across EUrope
QSens	German Future Cluster initiative
R&I	Research and Innovation
RBAC	Role-Based Access Control
REDCap	Research Electronic Data Capture
ReEIF	Refined eHealth European Interoperability Framework
RI	Research Infrastructure
ROGEN	EU-funded project on genomic research
SENASH	EU-funded project
SIPE	Electronic Prescription System (Romania)
SIUI	Single Integrated Information System
SME	Small and medium-sized enterprises
SNOMED CT	Systematised Nomenclature of Medicine- Clinical Terms
SOLE	Sanità On LinE (Emilia-Romagna region HIE)
SOP	Standard Operating Procedure
SRDC	Software Research, Development and Consultancy
TCP/IP	Transmission Control Protocol / Internet Protocol
TEHDAS	Joint Action Towards the European Health Data Space
TEHDAS2	Second Joint Action Towards the European Health Data Space
TLS/SSL	Transport Layer Security/SSL (modern and secure evolution of SSL)

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Abbreviation	Definition/Description
URL	Uniform Resource Locator
VELES	European Union–funded health innovation project and excellence hub
VTT	No description – company name
VWS	Ministerie van Volksgezondheid, Welzijn en Sport (Netherlands)
WGBO	Medical Treatment Contracts Act (Netherlands)
WHO	World Health Organisation
WP	Work Package
XCA	Cross-Community Access (IHE profile for query/retrieve-ing documents across different Domains)
XDS.b	Cross-Enterprise Document Sharing (b version)- IHE profile for sharing documents
XDS-I	Cross-Enterprise Document Sharing – Image (IHE profile for sharing images)
X-eHealth	Cross-border eHealth (Horizon 2020 project on interoperable cross-border health data exchange).

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EXECUTIVE SUMMARY

Interoperability in health data can be described as the ability of different health systems, organisations and applications to exchange, interpret and use health data in a coordinated manner. This ensures that information flows securely and meaningfully across borders and sectors. It enables seamless collaboration and continuity of care, supports research and innovation and facilitates informed decision-making while respecting privacy and data protection regulations.

Deliverable D4.2 is part of the PRECISEU project's Work Package 4- *Use of Health Data*, which looks to assess health system readiness for secondary use of data, define data management needs and support cross-border interoperability with the ultimate goal of supporting Personalised Medicine adoption by healthcare systems across Europe. More specifically, D4.2 is directly related to Task 4.3 (*Technical, Syntactic, and Semantic Interoperability: from standards to FAIR by design approaches*) which aims to define the PRECISEU approach to ensure interoperable, semantically consistent clinical data exchange through standardised terminologies and data models, while embedding privacy, security and FAIR principles by design.

D4.2 defines the Interoperability Framework for the PRECISEU project. It implements the objectives and tasks defined for WP4 (Use of Health Data) in the PRECISEU Grant Agreement (Grant Agreement No 101161301, section WP4), in particular Task 4.2 and Task 4.3, and responds to the commitment to deliver an interoperability framework for PRECISEU and its Joint Interregional Projects. The Framework covers different layers of interoperability enabling secure and seamless exchange of health data for primary and secondary use across EU member states in alignment with the European Health Data Space (EHDS) and the FAIR (Findable, Accessible, Interoperable and Reusable) principles. It is designed to help diverse stakeholders – such as researchers, healthcare providers, innovators, policymakers, data professionals (e.g., IT professionals and data managers/stewards)- work together more effectively by promoting interoperability at the legal, organisational, semantic and technical levels. By doing so, and despite it is originally depicted for the PRECISEU Project, The Framework supports the creation of a more connected, trustworthy and sustainable European ecosystem as a whole for health data exchange. The current deliverable numbering follows the updated DoA/IPR-AWP Y2, where the interoperability framework corresponds to D4.2.

The PRECISEU Interoperability Framework is built upon nine foundational principles that ensure secure, harmonised, ethical, and effective health data exchange across Europe. These principles are rooted in EU legislation, TEHDAS recommendations, FAIR data practices and international standards, ensuring technical robustness and social trust. The principles include 1)FAIR Data Principles, 2)Privacy by Design and Default, 3)Patient-Centric Data Control and Consent, 4)Cross-Border Data Sharing Enablement, 5)Security and Trustworthiness, 6)Interoperability by Design, 7)Transparency and Accountability, 8)Equity and Inclusiveness, and 9)Sustainability and Scalability.

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1. INTRODUCTION

1.1 The PRECISEU Project

PRECISEU is a five-year EU-funded project (2024–2029) coordinated by Biocat in Catalonia (Spain) that brings together 28 partners from 15 regions in 11 EU countries and Ukraine.

PRECISEU is a Regional Innovation Valley project supported by Horizon Europe, which connects innovation ecosystems across Europe to drive advancements in personalised healthcare, focusing on the exchange and scalability of advanced health data practices and the implementation of deep-tech healthcare innovations. The consortium includes Regional Authorities, clusters, universities, research institutions and other key stakeholders from nine European Union regions, joined by the Rivne region in Ukraine, aiming to foster cooperation for health innovation across the continent.

PRECISEU's overall objective is to increase the efficiency of the regional innovation ecosystems through strengthened collaboration and shared resources on strategic areas of regional strength and specialisation, enabling the development and implementation of innovative initiatives and facilitating the digital and sustainable transformation of European healthcare systems. The project has the ambition to:

- Accelerate the adoption of personalised medicine in Europe
- Connect innovation ecosystems across Europe
- Contribute to the transfer of practices and solutions among European regions
- Support the scaling-up of advanced technological innovations in the health sector, grounded in two pillars of personalised medicine: health data and advanced therapies
- Be a driving force, aligning the Personalised Medicine strategic agenda with the New European Innovation Agenda and the Smart Specialisation Strategy.

Among its other activities, PRECISEU funds specific Joint Interregional Projects (JIPs). These are collaborative initiatives that will connect European regional innovation ecosystems to implement and scale personalised medicine solutions sharing best practices, health data and advanced therapies across regions. JIPs will cover a broad spectrum of topics on the following domains:

- Use of health data for Research & Innovation (R&I) in compliance with the EHDS regulation
- Contribution to make Advanced Therapy Medicinal Products (ATMPs) sustainable and affordable
- Build cross-regional value chains on Personalised Medicine to be undertaken by research and innovation entities from participating regions

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- Contributions towards the PRECISEU project objectives.

Adopting the Framework standards, protocols and practices will help JIPs and stakeholders to enable secure, efficient and meaningful exchange of health data across systems, institutions and borders, helping to reduce fragmentation and inequalities in the adoption of personalised medicine across Europe.

1.2 Relevance/link with other EU initiatives

The PRECISEU interoperability framework is closely aligned with key European initiatives that aim to enable secure, ethical and efficient use of health data across borders. It serves as a bridge between strategic orientations and deep operational guidance, supporting the creation of a trustworthy and sustainable European health data ecosystem.

- **European Interoperability Framework:** The PRECISEU interoperability framework is structured around the European Interoperability Framework (EIF) layers *(legal, technical, organisational, semantic)*, which constitute its core pillars and guide the implementation of interoperability. This is also the interoperability approach considered under the EHDS.

- **European Health Data Space (EHDS):** The Framework contributes directly to the EHDS vision by promoting interoperability for both primary and secondary use of health data in line with its legal, technical and governance requirements.

- **TEHDAS Joint Action:** It reflects the recommendations developed within TEHDAS and TEHDAS2, particularly regarding stakeholder engagement, governance models and technical enablers for cross-border data sharing.

- **FAIR Principles:** The Framework incorporates the FAIR principles (Findable, Accessible, Interoperable, Reusable), which are essential for good data management practices. FAIR principles are increasingly required in EU-funded projects and research infrastructures. Tools like the ELIXIR RDMkit, FAIR Cookbook, FAIRsharing and the Health-RI FAIRmetroline are powerful resources which provide further information and recommendations.

- **EU Data Strategy:** It supports the broader goals of the European Data Strategy by fostering data availability, quality and interoperability across regions.

By aligning with these initiatives, The Framework helps stakeholders move from strategic intent to practical data interoperability implementation, ensuring that health data can be shared securely, meaningfully and in full respect of privacy and data protection regulations.

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1.3 Topics covered and Target users

This framework addresses the essential dimensions of interoperability required for a secure and meaningful exchange of health data across borders and sectors. It introduces a multi-layered approach that is further elaborated throughout the document encompassing legal, organisational, semantic and technical aspects. These layers reflect the complexity of enabling interoperability in practice across Europe, from regulatory alignment to data standards and system integration. Specific recommendations and tools for the different interoperability layers are provided in Section 5.2 of this Deliverable.

The Framework is intended to support a wide range of users involved in the design, implementation and governance of health data infrastructures. It is particularly relevant for researchers working with secondary use of data, policymakers shaping national, regional and European strategies, healthcare providers seeking to improve continuity of care and data professionals such as IT professionals developing interoperable systems and data managers/stewards responsible for overseeing the collection, curation, harmonisation and secure sharing of health-data under the FAIR principles.

The Framework should be consulted both during the planning and deployment of new health data projects and solutions as well as when evaluating or upgrading existing infrastructures. It also serves as a reference model for aligning with the European Health Data Space (EHDS) and the FAIR principles, especially in the context of EU-funded projects and cross-border collaboration.

1.4 Expected Impact

By providing a structured and actionable interoperability framework, this Deliverable aims to foster a more connected and trustworthy European ecosystem for health data exchange. It is designed to align partners from different regions in cross-border initiatives such as PRECISEU with the EHDS requirements and the FAIR principles, reduce fragmentation across systems and enable the secure reuse of health data for research, innovation and healthcare.

The Framework promotes transparency and collaboration among stakeholders, offering clear guidance on governance, compliance and technical integration. Ultimately, it supports the creation of a sustainable and person-centred model for health data sharing, where interoperability is not just a technical goal but a strategic enabler of better care, smarter policy and responsible innovation.

While the aim is to provide an Interoperability Framework for the PRECISEU project and the JIPs, The Framework will also help the understanding and improvement of Interoperability across other European projects in line with the EHDS requirements.

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2. PRINCIPLES AND OBJECTIVES OF THE INTEROPERABILITY FRAMEWORK

2.1 Key Principles

The interoperability framework contained in this Deliverable is informed by nine principles that together form the foundation for secure, harmonised, ethical and effective health data exchange across Europe. These principles reflect EU legislation, TEHDAS recommendations, FAIR data practices and international standards, ensuring that The Framework is technically robust, ethically grounded and socially trusted.

FAIR Principles (Findable, Accessible, Interoperable, Reusable)

Health data must be managed in a way that ensures its long-term scientific and societal value. The FAIR principles guarantee that data can be located through persistent identifiers and rich metadata, accessed under clear usage conditions, exchanged and integrated through common standards and reused for both clinical and research purposes. Applying FAIR principles ensures the reproducibility of data assets, which remain usable and reusable across borders, disciplines and time, while avoiding duplication and fragmentation.

Privacy by Design and Default

Privacy must be embedded into all systems, processes and policies from the very beginning. In line with the General Data Protection Regulation (GDPR), this means that the default settings of systems must minimise personal data exposure and that protective measures such as pseudonymisation or anonymisation, encryption and secure access are systematically applied. This principle ensures that citizen trust is maintained while enabling legitimate data use.

Patient involvement in Data Control

Patients and citizens should remain at the centre of data governance. This includes having transparent information about data use and outcomes generated by it, as well as mechanisms to withdraw or update consent. Patient empowerment strengthens trust and supports personalised medicine, where the individual's rights and choices guide how health data is used for care and research.

Cross-Border Data Sharing Enablement

Health and research data should flow seamlessly across Member States and Regions to unlock the full potential of personalised medicine. This requires harmonised standards, secure infrastructures and legal frameworks that allow mutual recognition of access applications and interoperability of governance models. Enabling cross-border collaboration ensures that expertise and resources are shared driving innovation, fostering knowledge and avoiding silos between ecosystems.

Security and Trustworthiness

Robust cybersecurity measures, strong authentication and audit mechanisms are essential to ensure responsible data handling. Stakeholders must be confident that data is stored, transmitted and used securely, with traceability for all actions. Trustworthiness is not only technical but also cultural: clear communication,

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visible safeguards and accountability contribute to building public and institutional confidence in health data exchange and visiting.

Interoperability by Design

Interoperability must be considered from the outset at legal, organisational, semantic and technical levels. Systems, processes and data models must be built with compatibility in mind rather than being retrofitted later. This principle supports efficiency and sustainability, avoiding costly fragmentation and enabling smooth integration and data sharing across regions.

Transparency and Accountability

Stakeholders must operate in an open and accountable manner, with clarity on how data is accessed, processed and used. This includes transparent governance models, clear documentation, regular reporting and oversight mechanisms that aim for compliance with ethical and legal standards across the regions. Transparency and accountability are key to building legitimacy and enabling trust among stakeholders.

Equity and Inclusiveness

Interoperability efforts must reduce inequalities rather than widen them. Solutions must be designed to benefit all Member States, regions and communities, including smaller healthcare institutions and underrepresented groups. Ethical, Legal and Social (ELSI) measures need to be put in place when designing any project, especially those involving cross-border collaborations, personal data and different types of institutions. This ensures that the benefits of personalised medicine are distributed fairly and ethically across Europe.

Sustainability and Scalability

The Framework must support long-term, cost-efficient and future-proof solutions that can expand as technologies evolve, datasets grow and policies develop, even well-beyond the project's ending date. Sustainability ensures continuity beyond initial investments, while scalability enables that successful solutions can be adopted widely. This means investing in architectures and governance models that are flexible, modular and adaptable, avoiding fragmented pilots and ensuring long-lasting impact across Europe.

2.2 Definition and relevance of Interoperability in health data

Interoperability is the ability for different systems, organisations and geographical jurisdictions (i.e., at local, regional, national and/or international level) to exchange, process, interpret and use data in an effective and efficient manner. This foundational notion has been formally structured at EU level through the European Interoperability Framework (EIF), which outlines four key layers - legal, organisational, semantic and technical — for enabling cross-border and cross-sector data exchange.

The concept of interoperability is therefore of utmost importance in the context of the use of health data across Europe. It fosters data-driven research, evidence-based policy making and improved healthcare services.

In the last few years, technological and scientific advances have translated into the generation of an ever-increasing amount of health data coming from various sources. These include but are not limited to clinical

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records, genomic information, medical imaging, sensor data from wearable devices or patient-reported outcomes. To support the implementation and adoption of personalised medicine, these diverse or multimodal datasets need to be integrated, connected and understood in a harmonised way for stakeholders to drive research and innovations as well as to deliver personalised diagnostics and treatments.

Taking into account the differences in the healthcare systems within the regions involved in the PRECISEU project, yet alone across all the EU healthcare systems, several aspects of interoperability must be considered to enable secure, meaningful and efficient exchange of data at a large scale, while respecting organisational, legal and ethical requirements.

2.3 Objectives

The PRECISEU project aims to ensure seamless and standardised data exchange across systems and regions, as this will enable effective collaboration within the personalised medicine and advanced therapy medicinal products (ATMPs) ecosystem. In this sense, the PRECISEU Interoperability Framework aims to support data harmonisation and integration in cross-border scenarios facilitating the secure and efficient use, sharing and analysis of health data.

Furthermore, The Framework seeks to foster trust and collaboration among the different stakeholders present in the health ecosystem when using and sharing data on personalised medicine, innovation and ATMPs across borders. By recommending common standards and interoperable models, processes, conditions and infrastructures, the PRECISEU Interoperability Framework will help a wide variety of stakeholders foster innovation, knowledge-sharing, support for value-based healthcare and evidence-based decision making in personalised medicine across Europe. Stakeholders include but are not limited to citizens, researchers and academic institutions, healthcare professionals and providers patients, public authorities, regulators and policymakers, innovators, health data access bodies and data managers/stewards, payers and health systems, startups and Industry, and Society at large.

2.4 State of the art in Health Data

To operationalise these principles, it is essential to understand the current landscape of health data generation and use. Tools such as the (CAMSS) methodology,- which evaluates standards and specifications in alignment with the EIF and the EU interoperability goal – are available to support this process.

Health-related information typically originates within the operational context of individual care processes. This context, often referred to as the domain of **Primary use of data**, is where observations and clinical data are generated, interpreted and applied to support diagnostic and therapeutic decisions. Starting from this domain, the need to ensure continuity of care requires that information is shared across different care providers and organisational settings.

To enable such sharing, it is essential that data and information- from which clinical insights are derived – are collected, accessible, interpretable and reusable by all relevant actors. This calls for a harmonisation effort that spans multiple layers of interoperability, each addressing distinct but interrelated aspects:

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- **Legal and ethical interoperability**, which safeguards patient rights and regulatory compliance
- **Organisational interoperability**, which aligns processes, roles and responsibilities
- **Semantic interoperability**, which guarantees consistent interpretation of content
- **Technical interoperability**, which ensures secure and reliable data transmission

This layered understanding also highlights the need for interoperability not only at the level of raw data, but across the entire continuum of clinical information. It is therefore essential that data is made interoperable and shareable across regions, systems and stakeholders, regardless of their technological architecture or geographical location and situated at regional, national or international level.

However, achieving interoperability requires not only a shared vision but also tools and methods that are appropriate to the specific layer (legal, organisational, semantic or technical), the object of exchange and the level of abstraction at which that layer operates. While the term *data* may be sufficiently precise at the legal level- where it often refers to categories of personal data and associated rights- it becomes increasingly ambiguous at lower levels. In the context of primary use, for instance, what is exchanged are often raw data that only acquire meaning when interpreted as information and further evolve into knowledge or clinical reasoning when integrated with the expertise and context of the stakeholders involved.

To better conceptualise this gradient of structure and interpretability, the metaphor of solid, liquid and gaseous data, as introduced by Rossi Mori and colleagues at MIE 2024[1], offers a valuable lens. *Solid data* are highly structured and codified- such as laboratory results, often numeric, or ICD codes- and are easily transmitted and aggregated. *Liquid data* retain structure, but require contextual information to be interpreted correctly, such as clinical observations or care plans. *Gaseous data*, finally, encompass narrative reasoning, uncertainty and tacit knowledge- elements that are essential for clinical understanding but difficult to formalise or transmit without significant loss.

This layered nature of health information highlights the limitations of purely code-centric approaches to interoperability and underscores the need for more nuanced, context-aware strategies- especially when aiming to support continuity of care, clinical decision-making or meaningful secondary use. Ensuring interoperability also across all three levels — solid, liquid and gaseous — is critical to enabling meaningful data exchange, supporting clinical decision-making and fostering continuity of care throughout the health system.

These three levels of data structure intersect with the four layers of interoperability present in this framework, each requiring distinct strategies for capture, representation and exchange. These can be materialised as rules, processes, shared standards, unstructured text to coded entries and numerical values, each requiring tailored interoperability strategies. This heterogeneity poses a concrete challenge for data sharing and reusability and

[1] The SLG Framework - Solid, Liquid, Gaseous States of Healthcare Information (link)

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calls for flexible yet rigorous approaches to ensure consistency and interpretability across systems and stakeholders.

Secondary use of data- defined in this context as the reuse of health data for purposes other than direct patient care, such as research, epidemiological analysis, innovation or health planning- also requires high levels of interoperability. In this context, data must often transcend the clinical specificity of individual cases to be aggregated, compared and interpreted on a broader scale. The coexistence of different goals between primary and secondary use imposes even stricter semantic and structural requirements.

Therefore, only a complete representation of interoperability allows data to be effectively leveraged in both domains without compromising meaning or quality. This dual perspective reinforces the need for flexible, scalable and semantically robust solutions. This challenge is particularly evident in cross-regional contexts, where harmonisation across diverse infrastructures, standards and governance frameworks becomes essential to enable meaningful data exchange and collaboration.

Moreover, these challenges are compounded by the fact that a substantial portion of currently available health data—acknowledging the inherent ambiguity of this term—is still recorded in free-text formats, lacking structured, coded or numerical representation. Regulation (EU) 2025/327 on the European Health Data Space (EHDS) defines personal health data in broad terms (Article 2) and explicitly includes medical reports (Article 14), without restricting its applicability to structured and coded data only. Therefore, while the project strongly promotes the adoption of internationally standardised and coded formats for recording health information, such a condition cannot be assumed as universally achieved.

As a result, the operational scope of this document must necessarily include personal health data that are not yet standardised or coded, in order to avoid arbitrarily excluding a substantial — and often predominant — portion of available health information. This inclusive approach ensures full alignment with the current regulatory framework and supports a realistic, progressive implementation of technological and governance solutions for the management and sharing of health data.

2.5 Diversity of Health Data across Interoperability Layers

As we move from the highest (legal) to increasingly detailed layers (e.g. technical) of data interoperability, the need to analyse the specific nature of the information generically referred as *data* becomes more pronounced. For instance, when addressing legal aspects such as the right of access to personal health information, the nature or format of the data — whether structured numbers, standardized codes or free-text records — makes little substantive difference. When it comes to technical interoperability, the approach must radically adapt to the specific format in which information is encoded, as each type requires distinct methods for processing, integration and exchange. Addressing the technical dimensions of sharing such information, the distinction becomes critical: handling a free-text document (written or audio/video-recorded), structured data or medical images in standardised formats requires to consider different approaches and solutions.

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3. METHODOLOGY

The PRECISEU Interoperability framework considered in this Deliverable, as well as other Deliverables from WP4, was informed by a multi-pronged methodological approach, combining desk research, expert engagement and cooperative validation. The process aimed to ensure both conceptual robustness and practical relevance across diverse health data contexts across European regions.

3.1 Literature and Policy Review

A structured review of EU policy, scientific and technical documents was conducted to identify existing models, frameworks and best practices related to data access, interoperability and secure processing in health across Europe. Results from the review were gathered and commented in regular meetings. As a result, a compilation of good practices, recommendations and relevant standards was obtained.

This review provided the basis for defining the interoperability layers of the PRECISEU Interoperability Framework and identifying critical enablers and barriers regarding data interoperability across Europe.

3.2 Domain experts interviews

To complement the desk research, a series of interviews was conducted with representatives from TEHDAS and other large initiatives and EU-funded projects as well as national authorities, who are expert in data access, data interoperability and secure processing domains. The interviewees comprised a Senior Lead at Sitra – Finnish Innovation Fund (and TEHDAS2 Coordinator), a Scientific data management specialist at CSC- IT Center for Science, a Health Innovation Consultant from Sciensano and the Acting Head of Data Services at Findata in Finland and more specifically for data interoperability, a Senior Researcher at SRDC (Software Research, Development and Consultancy Ltd) in Ankara, a Principal Scientist by VTT Technical Research Center of Finland and a Senior Scientist at IRPPS-CNR in Italy. The interviews took place in different dates between May and October 2025 and explored real-world challenges, expectations, tools and use cases related to data interoperability, cross-border and cross-sector health data exchange, access, processing and storage. Insights from these conversations were instrumental in refining the Framework's content and structure while ensuring its alignment with operational realities.

Findings from the literature review and interviews were considered and included in this Framework, which was then iteratively refined through internal expert consultations and feedback loops with external reviewers and the PRECISEU consortium. This iterative process ensures that the resulting framework is both theoretically grounded and practically applicable across a range of European health data ecosystems.

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4. INTEROPERABILITY FRAMEWORK FOR PRIMARY USE OF DATA

Primary use of data refers to the processing of health data within the context of direct patient care. According to the EHDS Regulation, *Primary use of electronic health data* means the processing of personal electronic health data for the provision of health services to assess, maintain or restore the state of health of the natural person to whom that data relates, including the prescription, dispensation and provision of medicinal products and medical devices, as well as for relevant social security, administrative or reimbursement services. In this context, interoperability specifically refers to the ability of health professionals and patients to access and share health information in real time, regardless of where the data was generated or stored.

The primary use of health data consists of an approach inherently person-centred, aiming not merely to treat diseases in the abstract, but to care for the individual patient in their specific clinical and personal context. Data are not typically collected and recorded according to a standardised model, but are primarily intended to support the health and/or care of a specific, "unique" natural person.

Moreover, healthcare data are often fragmented, unstructured and inconsistently coded across different hospital departments and national systems. As a result, clinical systems cannot exchange or interpret data reliably, especially across borders. This is a core barrier to personalised, interoperable care in Europe.

Interoperability ensures that healthcare providers can access, interpret and use health data seamlessly, enabling real-time, cross-border clinical decision-making, while empowering individuals to access and manage their health data effectively. Data should be collected for primary use under the FAIR principles (Findable, Accessible, Interoperable and Reusable). A FAIR-by-design data collection will allow for data accurately shared, understood and reused later, fostering care continuity, cross-border treatments and secondary uses like research or innovation while reducing duplication and increasing data quality from the start. Importantly, applying FAIR principles from the outset also enhances the primary use of data — supporting safer, more coordinated and person-centred care by ensuring that clinical information is readily available, interpretable and actionable at the point of care.

4.1 Structuring interoperability: from principles to practice

In a description that moves from general to specific — from theoretical principles to concrete technological implementation — the concept of interoperability, as previously described, can be structured across four main layers (aligned with the recommendations of the EIF):

a) Legal interoperability. It guarantees that the sharing of data across borders follows the applicable laws and regulations, both within and between the EU Member States.

   This includes compliance with the General Data Protection Regulation (GDPR) and with the European Health Data Space (EHDS) Regulation, as well as with relevant national legislation on health data use,

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informed consent and data subject privacy rights. The current European regulatory framework for health, starting with the GDPR and complemented by the EHDS Regulation, offers a robust foundation for the legal layer of interoperability concerning citizens' personal health information.

It is likely that further legislative alignment will be needed primarily at the national level, particularly in response to the One Health paradigm and the Patient-centred approach. These models promote integrated care pathways that transcend traditional sectoral and operative boundaries and require legal frameworks capable of supporting cross-domain data sharing, including health and social care. Crucially, this approach calls for a shift from treating isolated clinical conditions to taking holistic responsibility for the person — considering their medical, psychological and social dimensions as interconnected aspects of care.

To enable this, the legislations must evolve to reflect the complexity of real-world care delivery, ensuring that data governance supports ethically sound, lawful and interoperable information flows across sectors, regions and professions.

In this context, it may be necessary to further explore:

- A clearer definition of roles and responsibilities within the health and social care sectors;

- A more precise indication of access levels and permissions to specific subsets of a citizen's health information - both for social care professionals accessing health-related data and for healthcare personnel accessing information on the social support services that are active or required for the individual.

- The removal of unnecessary restrictions such as different interpretations of GDPR amongst countries - whether practical, regulatory or even only perceived - that hinder effective data sharing within healthcare, and the seamless integration of healthcare itself and social care.

This would contribute to a more coherent and ethically sound framework for cross-sectoral data sharing, aligned with the principles of interoperability and the broader goals of integrated care.

- The need to ensure greater consistency in the interpretation of European legislation (GDPR and EHDS for now and, in all likelihood, the AI Act in the future) by national authorities (e.g. EU Data Protection Authorities - DPAs).

A possible step towards this increased uniformity would be the creation of a single, logically structured repository that brings together:

- All documents and decisions issued by national data protection authorities (EU DPAs) and, in perspective, other EHDS authorised participants such as the HDABs (Health Data Access Bodies)

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- The official acts and guidance produced by the European Data Protection Supervisor (EDPS) and by the European Health Data Space Board (EHDS Board)

- Documents, reports and decisions issued by the offices and bodies established under the EHDS Regulation, including national digital health authorities and cross-border coordination entities. One key figure here is the EHDS Board, a new independent advisory and regulatory body that facilitates the exchange of data among member states and with the European Commission (EC). More information about the EHDS Board can be found in Articles 92 and 94 of the EHDS Regulation.

Starting from health-related data, this repository should support federated and topic-based querying, enabling users- potentially with the support of AI-powered search and classification tools- to retrieve all relevant decisions and documents issued by different authorities on a given subject. This would enhance transparency and accountability, foster alignment across Member States and facilitate the implementation of a coherent and ethically sound framework for data governance in the European Health Data Space. An enhanced harmonisation of consent-related rules and data collection requirements would also be advisable.

b) Organisational interoperability. It is about aligning and coordinating the processes, responsibilities and governance structures among the institutions that share data. It is an important aspect that fosters trust and facilitates collaboration and is based on the definition of roles and responsibilities as well as the use of shared policies or operating procedures, such as the IHE profile and the potential execution of inter-organisational agreements. Organisational interoperability must also engage healthcare professionals who play a critical role in applying shared procedures, managing patient data and ensuring that governance models are effectively translated into daily practice. Their active participation is essential to build trust, ensure consistency and bridge the gap between institutional frameworks and frontline care delivery. It refers to the way in which health administrations align their processes, responsibilities and expectations to achieve commonly agreed and mutually beneficial goals. For the primary use of health data, organisational interoperability ensures that the necessary workflows, policies and stakeholder collaborations are in place to support timely, accurate and secure data sharing. This requires clearly defined roles and responsibilities to support consistent data management, along with collaborative governance structures that facilitate joint decision-making and alignment on data sharing practices.

Active engagement and training of clinicians, technical staff and managers are essential to build capacity and promote effective adoption of interoperable systems. Additionally, coordinated management of clinical terminologies ensures semantic consistency across organisations, which is critical for delivering personalised medicine in a cross-border context.

At a higher level, cooperation policies — at all levels, including formal agreements, shared protocols and cross-border networks — can significantly boost organisational interoperability. One strong

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example of organisational interoperability in practice is the European Reference Network (ERN) ITHACA, which supports patients with rare congenital malformations and neurodevelopmental disorders. This network enables clinicians across EU countries to collaborate on diagnosis and care, often requiring access to genetic and clinical data from different national health systems. Well-coordinated processes, shared clinical practices, role clarity and a trusted governance model across multiple institutions and countries. For example, a clinician in Belgium may consult genetic specialists in France through the Clinical Patient Management System (CPMS)- a secure, EU-developed platform. To enable this:

- Governance agreements among ERN members define shared procedures, responsibilities and GDPR-compliant data handling protocols.
- Harmonised workflows are in place to guide how and when patient cases are submitted for cross-border review.
- Clear roles are defined: the local clinician leads case submission; ERN experts review and respond.
- Training and support are offered across all ERN centres to ensure consistent platform use and collaboration practices.

But organisational interoperability should not be limited to public administrations alone. It must encompass all stakeholders in the healthcare ecosystem — including private entities, academic institutions, professional associations and technology providers — to ensure a truly integrated and sustainable approach to data sharing. This requires not only institutional alignment, but also individual commitment: every person involved — not just every resource or role — must actively operate in accordance with shared principles and practices. Moreover, a cascading approach is essential, whereby organisational decisions and governance structures explicitly guide the adoption of semantic standards and the selection of appropriate technological solutions. This ensures that interoperability is not an accidental outcome, but a deliberate and structured result of upstream choices — from role definition and workflow design to terminology management and system architecture.

Strategic focus on Education, Training and Professionalisation of key roles

A key enabler is the integration of data sharing and foundational interoperability principles into university curricula and medical specialisation programs, improving hard and transferrable skills. Future clinicians, managers and technical professionals must be equipped to understand and communicate not only the value of interoperable systems, but also their complexity, constraints and operational requirements. Establishing advanced tools for clinical data exchange is suboptimal if everyday practice still relies on patients carrying paper documentation to bridge information gaps. This also includes recognising the limitations of spoken/written language and free-text documentation, which are normally adopted even if often ambiguous, difficult to process automatically and unsuitable for cross-border data exchange or machine interpretation. More education, training and professionalisation will

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improve the scarcity of interoperability experts within the data professionals' scope and, specifically in public organisations, shorten the gap between private and public organisations.

Structured Data as a bridge

To overcome these barriers, starting from the organisational level, it is necessary to promote the use of structured, coded and numerical data, aligned with international standards such as SNOMED CT, LOINC, ICD and others – which represents the *solid* data, as previously indicated. These formats enable semantic clarity, facilitate automated processing and support safe and meaningful data exchange across borders.

Procedural Alignment

Effective data sharing requires more than only technical tools. It demands a parallel process of clinical and procedural harmonisation, including shared clinical workflows and protocols and agreed-upon datasets and terminologies.

While the adoption of IHE profiles at the European level is a valuable first step, it remains partial. A broader effort is needed to align clinical practices and semantic frameworks across institutions and countries. At this layer, the engagement of patient and civic associations must also be acknowledged as essential — both to promote awareness and trust in data sharing and to integrate patient perspectives into semantic definitions and governance frameworks. Initiatives such as European Reference Networks (ERNs) and the use of the CPMS platform for cross-border clinical collaboration are highly valuable and should be actively encouraged. They represent operational agreements that extend cooperation beyond national borders, enabling clinicians and institutions to collaborate across Europe. However, it is important to clarify that these initiatives do not rely on technical interoperability in the strict sense. Patient data are not accessed or exchanged through interoperable systems, but rather manually replicated within the CPMS platform by the clinicians involved. The collaboration is based on expert consultation, not on the provision of digital services directly accessible to the clinical teams responsible for patient care. In this sense, the interoperability is organisational and procedural but manual, not technical, systemic or automated. Their success nonetheless highlights the importance of structured governance and procedural alignment, which can serve as a stepping stone towards broader, standards-based interoperability frameworks.

c) **Semantic interoperability.** It ensures that the meaning of the data is preserved so that it can be interpreted in the same way across systems. It is the domain in which the views of all the interviewed experts converge the most and which is unanimously regarded as essential. It involves the use of standard medical terminologies (e.g., SNOMED CT, LOINC, ICD-10) that provide shared vocabulary to structure the data in a way that is understandable across systems. Because different systems may use different terminologies, tools such as ontology mapping are used to translate or align concepts. It ensures that the precise format and meaning of exchanged data and information is preserved and understood throughout exchanges between parties. PRECISEU adopts and advocates the IHE Terminology Sharing White Paper to establish a federated model of terminology services, which is critical for semantic interoperability across different clinical systems. This architecture supports multiple terminology providers (national, regional or local), enabling distributed management while maintaining semantic consistency across systems. Its objective is to ensure that clinical data are

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correctly understood across different systems, languages and jurisdictions, facilitating interoperable and cross-border healthcare. Most experts recommend avoiding local solutions in favour of international standards; however, some advocate a pragmatic approach, based on partial solutions to be progressively integrated as objectives become clearer and more specialised. This approach involves structured authoring, publishing and discovery of artefacts using HL7® FHIR® terminology services. Terminology repositories store the terminological artefacts in FHIR® format, supporting versioning, lifecycle management and multilingual content, while terminology central registries facilitate discovery of available terminologies and versions, acting as a directory for consumers (clinical systems) to locate appropriate terminologies. Experts working mainly in the field of research tend to emphasise the distinction between standards typical of primary use (such as FHIR®) and those more suitable for secondary use (such as the OHDSI OMOP CMD). Semantic bridging between national and international terminologies is also crucial. Tools for creating and validating mappings (e.g., between SNOMED CT and ICD-10 or LOINC and local laboratory codes), using platforms like ART-DECOR or Snapper are essential for supporting cross-border patient mobility and care continuity.

A practical European implementation reflecting the principles of the IHE terminology sharing profile is the MyHealth@EU initiative, coordinated by the European Commission. MyHealth@EU enables cross-border exchange data (e.g., patient summaries and ePrescriptions) among EU member states. Different European countries use varying clinical terminologies and coding systems, such as SNOMED CT or ICD-10 and localised laboratory or medication codes. By enabling a federated terminology service MyHealth@EU allows to validate and translate clinical codes in real time as documents are exchanged. This federated terminology approach ensures that healthcare providers across borders can accurately interpret and act on clinical data regardless of the original coding system, supporting continuity of care and patient safety during cross-border treatment. But semantic interoperability goes beyond terminology alignment; it requires shared information models, consistent data structures and harmonised clinical workflows that preserve meaning across systems and contexts. As indicated referring to MyHealth@EU, this is essential to enable continuity of care and patient mobility within the European health ecosystem. It is worth noting that semantic alignment is performed dynamically during data exchange, rather than being embedded within the source systems — highlighting the need for upstream semantic integration. Enabling tools to achieve this goal can surely be the adoption of a federated model of terminology services- as proposed in the IHE Terminology Sharing White Paper for primary use of data and in the TEHDAS Recommendations for secondary use – and technically the use of HL7® FHIR® terminology services for structured authoring, versioning, multilingual content and lifecycle management of terminological artefacts.

Central registries and repositories to support terminology discovery and access, with a semantic bridging between local, national and international terminologies (e.g., SNOMED CT ↔ ICD-10, LOINC ↔ local codes) need to be available.

Specific semantic requirements, however, vary also depending on the nature of the data:

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- Numeric data → units of measurement, reference ranges, measurement methods
- Coded data → standardised taxonomies, terminologies or ontologies
- Omics data → biomedical ontologies
- Core Clinical Datasets → Defined shared data sets for specific science domains that include all elements relevant for research in their field (based on IHE profiles, openEHR archetypes, HL7 FHIR models enriched with semantic and procedural components).

To address those goals it is needed to evaluate the readiness level of healthcare organisations in adopting semantic standards and interoperable processes and to promote Living Labs- user-centred, open innovation ecosystems based on a systematic user co-creation approach, integrating research and innovation processes in real-life communities and settings- and Controlled Experimentation Test environments- controlled setup or system used to conduct testing - to validate semantic models, shared datasets and cross-border data flows. There is also a need to manage free-text reports, multimedia (images, audio, video) files and PGHD (patient generated health data).

We must nevertheless address many situations in which data are still unstructured, where "clinical information systems contain heterogeneous data, much of them still in unstructured form, such as narrative reports (imaging reports or discharge summaries), notes and correspondence with often a lack a complete view since these data are scattered between different sub-systems within different departments or healthcare provider organisations and not indexed thanks the consistent use of shared terminologies"[2]

In all these situations a deeper use of Artificial Intelligence (AI), AI techniques and natural language processing (NLP) algorithms to transcode natural language into standardised terminologies and extract semantic meaning from unstructured or multimedia data could be employed – taking into consideration the potential ethical and legal connotations. In all these cases- unlike the approach to semantic interoperability, which is typically considered only at the moment of data exchange- it is instead appropriate to perform recognition and transcoding already at the time of unstructured data generation. This allows the system to prompt the output of the coding to the author to review and validate the proposed classification, to make any necessary corrections and thereby contribute to the refinement of the system's training process (human-AI interaction).

Finally, if standards, automation and cultural progress fail to achieve the expected semantic alignment, it may be necessary, as a temporary and last-resort option, to rely on dedicated professionals who can act as interpreters and semantic mediators across different actors.

d) Technical interoperability. It focuses on how the systems can connect and share data at a basic level. It can be considered as the technical language that will support syntactic interoperability (so important

[2] IHE Terminology White Sharing Paper

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that in some publications and reports[3] it is even described specifically), which defines the data exchange and its structure, and related interconnection, integration, accessibility and presentation of data. This covers the physical and software infrastructure needed for systems to exchange data, such as established formats, tools and protocols and the corresponding syntactic interoperability. These include:

- Communication protocols that define how the data is transmitted between systems (e.g., HTTPS, MQTT, HL7 v2 MLLP)
- Data transport standards that set how data is packaged and sent (e.g., TCP/IP, DICOMweb)
- Data formats and syntactic standards that delineate how the data is structured and formatted (e.g., HL7 FHIR, DICOM, OMOP) and also the standardised way in which such structure conveys its intended meaning
- Application Programming Interfaces (APIs) that enable systems to request and exchange data (e.g., FHIR RESTful APIs, OpenEHR APIs)
- Standard interfaces for data integration and access that consist in technical frameworks that enable the different systems to connect to each other and exchange data (e.g. IHE profiles, Health Information Exchange interfaces, OpenHIE)
- Data security (e.g., TLS) and encryption standards (e.g., AES) that ensure data confidentiality, integrity, as well as secure transmission, storage and access
- Infrastructure components that consist in the core hardware and software systems that enable data storage, processing and exchange (e.g., cloud platforms, health data networks, firewalls).

This layer provides the foundation upon which semantic and organisational interoperability can be built, enabling not just data exchange, but meaningful and actionable communication across systems and institutions. It means making sure different healthcare systems can connect and share data smoothly across systems, countries and regions using common standards and tools. For the primary use of data this is essential to ensure that systems understand and use the data correctly in real time for direct patient care, diagnosis and treatment.

Aspects of technical interoperability include interface specifications, interconnection services, data integration services, data presentation and exchange and secure communication protocols. In that sense, the EIF recommends the use of open, widely adopted technical standards and protocols to enable secure, scalable and reliable data exchange. To ensure consistent data structuring and exchange, PRECISEU promotes the use of HL7® FHIR® as a syntactic foundation for clinical data models.

[3] such as in TEHDAS report

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Standardised FHIR profiles and implementation guides allow systems to exchange interoperable, machine-readable resources such as patient details, diagnostics or medication.

Also, the EIF recommends using information systems and technical architectures that cater for multilingualism when establishing a European public service. Decide on the level of multilingualism support based on the needs of the expected users. Technical interoperability should be ensured, whenever possible, via the use of formal technical specifications.

Conformance testing is a core technical enabler. PRECISEU recommends the use of Gazelle testing tools for validating IHE profile implementations and FHIR validators to ensure adherence to international profiles.

IHE profiles like XDS.b (document exchange), PIX/PDQ (patient identity) and XCA (cross-community access) are also leveraged for transnational clinical data sharing. However, some of these profiles, such as XDS.b, primarily define the rules and protocols for document exchange, without enforcing constraints on the internal structure or language of the documents themselves. As a result, clinical content may be written in free-text and in a specific national language, making it potentially ambiguous or entirely unintelligible to care providers in other countries. A purely technical interoperability solution may ultimately prove ineffective in achieving its intended goals, unless it is complemented by semantic and organisational alignment.

In addition to these elements, the technical layer must also support robust access control mechanisms that regulate who can view, modify, or share specific health data. This includes identity verification, role-based access policies, audit trails and consent enforcement technologies. These features are essential to uphold privacy, ensure accountability and maintain trust in digital health ecosystems.

Data shared in primary care contexts must be protected against data misuse, alteration or unauthorised access using robust technical and organisational controls. PRECISEU requires the use of secure communication protocols (TLS/SSL), federated identity frameworks (eIDAS, OAuth 2.0) and access control mechanisms (ABAC/RBAC). Consent directives must be enforced through integrated consent management systems and all transactions must be logged for auditability and trust.

This layered approach provides a comprehensive and actionable framework for implementing interoperability in line with the European Interoperability Framework (EIF) and its refinement for the health domain (previously ReEIF and now EEHRxF , MyHealth@EU and ESHIA) ensuring coherence between policy, governance, semantics and technology.

A concise overview of the main European initiatives developed over time to foster integration and interoperability in healthcare can be useful. This outline highlights the evolution of frameworks and regulations, showing how the approach has gradually moved from general guidelines to binding standards and operational infrastructures.

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Period		Initiative	Reference
2004	EIF v1 (IDABC)	First framework for eGovernment	https://interoperable-europe.ec.europa.eu/sites/default/files/inline-files/EIF%20V1.0.pdf
2010	EIF v2	Update version of EIF including openness and reuse principles	https://interoperable-europe.ec.europa.eu/sites/default/files/inline-files/EIF%20v2_1.pdf
2013	EHealth EIF	Application of EIF to healthcare Definition 4 layers	https://www.digitalhealthnews.eu/images/stories/pdf/eif_vision.pdf
2015	reEIF	Refined version of eHealth EIF. Concrete examples (patient summary, ePrescription)	https://www.xt-ehr.eu/glossary/refined-ehealth-european-interoperability-framework/
2017	EIF v3	General framework for all public digital services	https://ec.europa.eu/isa2/sites/default/files/eif_brochure_final.pdf
2021	TEHDAS Joint Action	Recommendations on governance and secondary use of health data	https://tehdas.eu/tehdas1/
2024	TEHDAS2 Joint Action	Prepares the ground for the harmonised implementation of the secondary use of health data	https://tehdas.eu/
2025	EHDS	Established by Regulation (EU) 2025/327 and published in March 2025	https://eur-lex.europa.eu/eli/reg/2025/327/oj/eng
2025	ESHIA	Alliance for health standard	https://ehr-exchange-format.eu/working-on-ehrxf/eshia/
2027	EEHRxF	European Electronic Health Record exchange Format	https://ehr-exchange-format.eu/
2027	MyHealth@EU	Exchange infrastructure for primary use of health data	https://health.ec.europa.eu/ehealth-digital-health-and-care/digital-health-and-care/electronic-cross-border-health-services_en
2029	HealthData@EU	Exchange infrastructure for secondary use of health data	https://acceptance.data.health.europa.eu/healthdata-central-platform?locale=en

Table 6. Main European initiatives to foster interoperability in healthcare

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5. INTEROPERABILITY FRAMEWORK FOR SECONDARY USE OF DATA

The **secondary use of health data** refers to the processing of personal electronic health data for purposes other than direct patient care. According to the EHDS Regulation (Regulation (EU) 2025/327, Article 53), such purposes include scientific research, health statistics, planning and management of healthcare systems, training, policy-making, safety of medicinal products and medical devices, as well as quality and safety assurance of healthcare services. Secondary use requires data to be harmonised and made interoperable in order to be meaningfully analysed at scale, while respecting ethical principles and personal data protection.

In this secondary use of data context, interoperability refers not primarily to real-time sharing, but rather to the ability to integrate, compare and interpret data from heterogeneous sources, often distributed across different organisations and Member States. High-quality, standardised and ethically compliant health data at the point of care (primary use) cannot directly ensure that this data is structured and enriched in a way that also supports its subsequent secondary use for research, innovation and policy development. By harmonising data capture processes across systems and regions, The Framework enables integration, interoperability and reuse of data.

Technical and semantic interoperability are therefore essential to ensure that data collected in local clinical settings can be reliably reused to generate scientific evidence, support innovation, improve health policies and promote continuous learning within different health systems. This secondary use of data often also consists of situations involving the integration of information from different sources, bringing together clinical data from diverse systems, not necessarily homogeneous or even not necessarily based on the same coding paradigm. The adoption of common data models (such as OMOP CDM) and shared standards (e.g., HL7 FHIR, SNOMED CT) helps overcoming fragmentation and enables the creation of federated ecosystems where data can remain locally stored, but are securely and transparently accessible and queryable, in accordance with FAIR principles and the governance framework set out in the EHDS Regulation. Organisational and legal interoperability are also essential, as they enhance alignment in laws, consent, governance and organisational processes so data can be shared, trusted, and reused legally, ethically and effectively across institutions. As a result, interoperability for the secondary use of data is a strategic enabler of evidence-based, equitable, sustainable and person-centered healthcare, which is key to PRECISEU.

5.1 Interoperability and the Data Life Cycle

The Data Life Cycle (DLC) considered in this Interoperability Framework describes the process that the different actors interacting within HealthData@EU should follow once data collected for primary purposes is made available for secondary uses. It comprises the *data preparation* phase and the *user journey* phase. The former includes the data or metadata collection from primary sources, the standardisation for interoperable [primary or mainly] secondary use and the publication steps to make them easily discoverable; the latter depicts the stages of the user journey, from data discovery to data finalisation. It covers how to discover and request access, use the data and finalise its use, including returning intermediate outputs and enriched datasets to the

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data-preparing institutions. The DLC promotes interoperability by preparing data in standardised, compatible formats for easy sharing and reuse and by guiding users on how to consistently find, access, use and return it across systems.

Steps of the Data Life Cycle

- **Collection**: Obtain high-quality, standardised and ethically compliant health data while ensuring that this data is structured and enriched in a way that supports its subsequent use for care, research, innovation and policy development. By harmonising data capture processes across systems and regions, The Framework enables integration, interoperability and reuse of data.

- **Standardisation**: When applicable transform raw data into consistent, reusable formats using agreed standards.

- **Publication:** Make data available for discovery and reuse across borders through trusted and structured platforms in line with the FAIR principles.

- **Discovery**: Allow users (researchers, clinicians, policymakers) to find relevant datasets and metadata.

- **Access**: Provide authorised users with secure and ethical access to health data by implementing [in-border or] cross-border access procedures aligned with EHDS.

- **Use**: Enable collaborative data analysis, linkage and interpretation of harmonised datasets to generate research insights.

- **Finalisation**: Share research outcomes and ensure long-term availability.

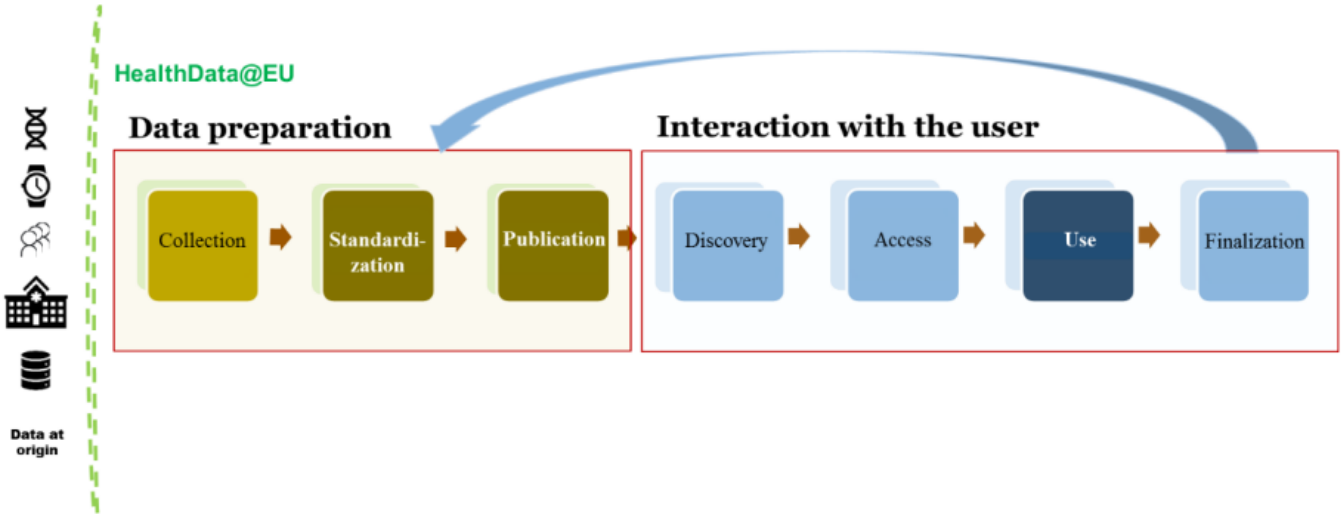

Figure 1. Data Life Cycle (source: TEHDAS2)

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The diagram omits the arrows that show the many feedback loops in the DLC. Inevitably, after we present some observations to the user based on data we generated, the user asks new questions and these questions require collecting more data or doing more analysis[4].

When a project or research yields positive results, it may also be useful to establish a global feedback mechanism that extends the dataset collected for the primary use, in accordance with the findings of the specific research that achieved a successful outcome.

Importance of the DLC for PRECISEU

The Data Life Cycle plays a central role in the PRECISEU project by providing a structured framework for managing health data across regions and ensuring effective collaboration among different institutions and stakeholders, allowing data to be seamlessly shared and reused across diverse systems and regions. In PRECISEU, the DLC supports cross-regional data sharing and reuse by aligning technical, semantic, legal and organisational interoperability layers across all stages, from data collection and curation to access, analysis and reuse, so that health data can move securely, be understood consistently, comply with regulations, and be operationally usable for personalised medicine across Europe. This is crucial for the JIPs because partners operate under different legal frameworks, organisational practices, data standards and technical infrastructures, and aligning the DLC and interoperability layers ensures health data can be shared, trusted, and reused across regions without legal risk, misinterpretation, or operational barriers, enabling meaningful collaboration and comparable results.

Mapping DLC phases to Interoperability Layers

Regardless of the sequence in which DLC phases occur, which may vary depending on context, purpose, or system architecture, each phase of the data lifecycle can be meaningfully associated with a dominant interoperability layer, reflecting its core operational and regulatory requirements. While multiple layers may be involved, the following mapping identifies the primary one for each phase:

DLC Phase	Main Interoperability Layer	Rationale
Collection	Technical	Data acquisition systems, structured input interfaces, device integration.
Standardisation	Semantic *(with strong organisational involvement)*	Terminologies, ontologies, metadata alignment, conceptual models.
Publication	Organisational	Governance, editorial roles, authorisation processes, anonymisation / pseudonymisation.
Discovery	Semantic	Indexing, semantic search, interpretability across domains.
Access	Legal	Access rights, declared purposes, compliance with GDPR and EHDS.

[4] Jeannette M. Wing 2019 (link)

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DLC Phase	Main Interoperability Layer	Rationale
Use	**Legal** *(with strong technical involvement)*	Lawful processing, reuse conditions, but also analytical environments, controlled infrastructures and audit mechanisms.
Finalisation	**Legal** *(with increasing technical relevance)*	Retention, erasure, anonymisation, supported by archiving systems and logging tools.

Table 7. DLC phases and interoperability layers

Notably, the phases of standardisation and collection may be intentionally inverted: in certain contexts, data collection is carried out only after the applicable standardisation methods / data model have been defined, ensuring consistency, semantic alignment and compliance from the outset.

The DLC phases in Secondary Use of data

While Data collection is mainly associated with primary use, as it is closely linked to the original context in which the data is generated (e.g., clinical care, direct research, administration), standardisation may apply to both primary and secondary use and in the sense indicated within the DLC framework, it finds its most appropriate meaning in the latter.

Generally, data recorded for primary use follow their own model, which may not correspond to the one required for research purposes. Therefore, the standardisation phase – although present in both types of data use – may need to be replicated, in order to align the data with the model agreed upon for the specific type of secondary use.

The subsequent phases of the data lifecycle, i.e. publication, discovery, access, use and finalisation, pertain to both primary and secondary use, since data may be repurposed for objectives beyond their initial scope, such as research, planning, innovation or policy-making, in compliance with applicable regulations. It could also be observed that, while the collection phase typically occurs in a targeted manner and refers to an individual care recipient, the modalities of data search, access and use differ significantly between primary and secondary use.

In primary use, data access generally occurs in a direct and patient-centred way, driven by immediate clinical or possibly administrative needs. In contrast, secondary use more commonly involves searching for data based on general criteria, such as pathologies, ongoing, completed or discontinued therapies or care processes delivered or underway, which allow the identification of cohorts of individuals matching those characteristics. Only then is a targeted retrieval of relevant data performed, which, in the context of secondary use, may pertain to narrower informational domains than those typically required for primary use.

These two distinct modalities of data access and use involve different levels of reference to the interoperability layers.

Important role of Data Publication

Data preparation and its outcome, data publication at the point of collection play a foundational role in ensuring quality, traceability, reproducibility, data verification and enrichment, and future usability.

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Data preparation should not be considered by default as part of the initial phases of the data lifecycle, nor as inherently belonging to the publication phase. Rather, it may be strategically positioned, including as a preparatory step for publication, depending on the specific context, objectives and system architecture. It is a case-by-case decision to adopt the most suitable strategy, bearing in mind that anticipating data preparation can help streamline and accelerate data availability, particularly in distributed or federated environments. This anticipatory approach requires the adoption of a unified or at least shared and compatible semantic framework across both primary and secondary use, in order to ensure interpretative consistency, interoperability and reusability.

Indeed, early-stage publication, even if partial, supports discoverability and reuse, especially when data is structured and semantically aligned from the outset. This enables timely access, facilitates cross-domain integration and reduces the burden of downstream harmonisation.

A distinct case, both in terms of publication and in the preparatory phases of data collection and standardisation, concerns the sharing of data from previous clinical trials.

This form of sharing, foreseen by art. 51 of the EHDS Regulation, is intended to resolve the regulatory limbo created so far by uncertainties in the interpretation of the GDPR.

In this context, the data lifecycle takes on specific characteristics: the intended use is entirely secondary from the outset, and therefore data preparation and publication are directly shaped by the needs of the specific research that will reuse the data.

This differs markedly from situations where data are collected for primary purposes and only later repurposed, in which case collection and publication cannot be "specific", as they occur before the objectives and informational requirements of any future secondary use are known.

Data preparation and publication phase should embed:

- Legal compliance (consent, lawful basis) - Interviewees highlighted that legal compliance must be embedded already in the data preparation phase, not only at publication. It is an enabler for reuse and interoperability, requiring documentation, traceability and semantic compatibility with GDPR and EHDS. Compliance is part of the system architecture and a driver of stakeholder trust. Importantly, without legal compliance, data of interest cannot be reliably discovered or accessed, making it a prerequisite for effective data sharing and reuse.

- Organisational validation (roles, authorisations) - at this layer data preparation and publication are not merely technical tasks, but require structured governance, clear responsibilities and coordinated workflows. They must be embedded into institutional processes that ensure accountability, quality, and transparency. Organisational interoperability is essential, as highlighted by the EHDS, which mandates coordinated procedures for secondary use. Ultimately, organisational choices about when and how to prepare and publish data reflect strategic objectives and build stakeholder trust.

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- Semantic alignment (terminologies, metadata) - semantic alignment constitutes the foundation of health data interoperability. The adoption of standardised terminologies (such as SNOMED CT, LOINC, ICD) and shared metadata schemas (DCAT-AP, HealthDCAT-AP for health) is not an optional technical choice, but a necessary condition to ensure that prepared and published data are understandable, comparable, and reusable across different contexts. Semantic alignment must be embedded from the earliest stages of data preparation, through mapping, normalisation, and annotation processes that ensure terminological consistency. Without a common language, data remain incomprehensible silos, undermining any sharing effort. The EHDS emphasises the need for rich and structured metadata to facilitate data discovery and interpretation, making semantic alignment a pillar of quality and reliability for published resources.

- Technical conformity (formats, APIs) - Technical conformity represents the infrastructure layer that makes interoperability operational. Interviewees highlighted that adopting standard formats (such as HL7 FHIR, DICOM, at least structured CSV) and standardised programmatic interfaces (RESTful APIs, secure protocols) is essential to ensure that prepared data can be effectively accessed, exchanged and integrated into recipient systems. Technical conformity is not only about format choice, but also includes aspects of security, access traceability and compatibility with existing infrastructures. The EHDS explicitly requires harmonised technical standards for secondary use, establishing that data publication must occur through technically compliant and interoperable channels. Without technical conformity, even semantically aligned and legally compliant data remain inaccessible, highlighting how this level is crucial for the practical realisation of the health data ecosystem.

5.2 Recommendations & Tools enabling interoperability in secondary use

The EU mainly adopts a standards-agnostic approach, defining functional, semantic, technical, organisational and legal interoperability requirements that EHR systems and data infrastructures must meet. Within this framework, several standards may be used by Member States or system providers as an implementation option, provided they support the required interoperability, data quality, security and cross-border exchange objectives. In practice, EU-level interoperability efforts focus on common exchange specifications and profiles and on alignment with recognised international standards, leaving flexibility for national and project-level choices.

Legal Interoperability

Recommendations, Resources & Tools

- Ensure GDPR-compliant data collection processes and tools, including informed consent via dynamic consent systems compliant with GDPR requirements; this comprises clear legal bases for processing, informed and explicit consent and full support for data subject rights.

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- Establish clear data ownership, accountability agreements and data stewardship responsibilities.
- Comply with national and EU-level legal requirements, including those of the European Health Data Space (EHDS).
- Secure necessary ethical approvals for clinical and research data collection and for processing sensitive data across borders.
- EHDS Preparatory Guidelines: while not formalised into tools yet, these include guidance on how to align national systems with EHDS expectations, including access permits and data altruism mechanisms. For further information, please refer to TEHDAS as one of the main sources of EHDS Preparatory Guidelines.
- Use harmonised licensing models to ensure data reuse across EHDS participants. Use open licenses (e.g. CC-BY, CC0) where possible and clearly specify legal restrictions where access is limited.
- Use transparent information on data access conditions, roles and user rights in a standardised EHDS-aligned manner.
- Ensure cross-registry compatibility and standard data fields by aligning legal and structural definitions of these fields to enable data exchange across registries and regions.
- Apply uniform rules for standardised access and EHDS data permits.
- Apply the Data minimisation principle by ensuring only strictly necessary data are shared.
- Make sure that data pseudonymisation and anonymisation measures are in line with national and regional requirements. Adopt the European guidelines for data pseudonymisation when required.

Main standards enabling legal interoperability in Europe are presented in Table 8 and Table 9 below:

Standard, Framework, Environment	Name	Link	Additional layer(s) & Notes
GDPR	General Data Protection Regulation	https://gdpr-info.eu/	Organisational; technical
AI Act	Artificial Intelligence Act	https://artificialintelligenceact.eu/	Technical; organisational

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Standard, Framework, Environment	Name	Link	Additional layer(s) & Notes
DGA	Data Governance Act	https://eur-lex.europa.eu/eli/reg/2022/868/oj/eng	Technical; organisational
MDR IVDR	Medical Device Regulation In Vitro Diagnostic Regulation Regulation	https://health.ec.europa.eu/medical-devices-sector/new-regulations_en https://eur-lex.europa.eu/eli/reg/2017/746/oj/eng	Technical; organisational
Cybersecurity	NIS2- Network and Information Security Direct.2 CSA – cybersecurity act Cyber Solidarity Act	https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32022L2555 https://eur-lex.europa.eu/EN/legal-content/summary/the-eu-cybersecurity-act.html https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=OJ:L_202500037 https://eur-lex.europa.eu/eli/reg/2025/38/oj/eng	Technical; organisational
Data Act (rules on fair)	Regulation (EU) 2023/2854 on harmonised rules on fair access to and use of data	https://eur-lex.europa.eu/eli/reg/2023/2854/oj/eng	Organisational; technical
EHDS	European Health Data Space Regulation	https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=OJ:L_202500327	Organisational; technical

Table 8. Main standards enabling legal interoperability in Europe (Regulations and Directives)

Regulations, Directives and Guidelines do not have the same legal effect and should be considered in order to prioritise or determine compliance to each legal instrument. Regulations are harmonised legal instruments that have direct effect within the European Union and must be followed according to their rules by all Member States. Directives, on the other hand, set rules that the Members States must implement to their national system. Therefore, a Directive is only applicable in a Member State if it has been transposed to the national system, and each national system may diverge or present differences, as there is a level of discretion as to how each Member State can transpose a Directive. Lastly, guidelines and other forms of legal guidance are suggestions and interpretations, usually made by authorities with competence over a specific field, that help users understand how authorities may implement and enforce the law. Nevertheless, these instruments are not legally binding, which allows courts to determine a different interpretation.

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Standard, Framework, Environment	Name	Link	Additional layer(s) & Notes
ISO/IEC 42001:2023	Information technology — AI — Management system	https://www.iso.org/standard/42001	Technical; organisational
ISO 14971 IEC 62304	Medical Devices risk management Medical Device Software Life Cycle Processes	https://www.iso.org/standard/72704.html https://www.iso.org/standard/38421.html	Technical; organisational
Pseudonymisation IEEE 7000 series	Guidelines for pseudonymisation Addressing Ethical Concerns during System Design	https://www.edpb.europa.eu/our-work-tools/documents/public-consultations/2025/guidelines-012025-pseudonymisation_en https://www.iso.org/standard/84893.html	Technical; organisational

Table 9. Main standards enabling legal interoperability in Europe (Guidelines)

Organisational Interoperability

Recommendations, Resources and tools

- Clearly define institutional workflows, responsibilities and governance for data collection activities.
- Provide training and capacity building for staff involved in clinical and research data entry.
- Align data collection protocols across institutions and regions participating in PRECISEU (and beyond) to ensure consistency.
- Implement quality control procedures and feedback loops to monitor data completeness and accuracy at the source.
- Data Stewardship Guidelines: define role definitions and workflow templates to help institutions assign clear responsibilities in the data collection process. Some examples of Guidelines are The Research Data Management toolkit for Life Sciences (RDMKit), FAIR Cookbook and FAIRsharing from ELIXIR, the Turing Way book, the Data Stewards' Best Practice from the University of Harvard or the Handbook for Adequate Data Management and FAIRmetroline from Health RI.

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- Implement Standard Operating Procedures (SOP) Templates for Clinical and Research Data Capture that ensure harmonisation across collecting sites and promote consistency.

- Training Toolkits: provide and use online resources and certification materials for data collectors and stewards, to ensure understanding of FAIR principles, GDPR and the correct use of tools like REDCap or FHIR.

- Quality Monitoring Dashboards (e.g., OHDSI Achilles): implement automated dashboards to assess data quality, completeness and structure after collection and transformation into OMOP CDM.

- Maintain and document data catalogues in a standardised format to ensure discovery and management across Regions. The DCAT-AP (data domain neutral) and the HealthDCAT-AP are considered the *de facto* to be used standards for data catalogues in the EU.

- Enhance data visibility by promoting transparent metadata and indexing practices to facilitate cross-border access.

- Enable federated access and trusted research environments to allow secure, interoperable analyses through shared platforms without moving sensitive data.

- Standardise Data Access Committees and Data Access Bodies workflows to ensure consistent, compliant and operational review processes.

- Encourage data quality and reuse.

Main standards enabling organisational interoperability in Europe are presented in Table 10 below:

Standard, Framework, Environment	Name	Link	Additional layer(s) & Notes
IHE	Integrating Healthcare Enterprise	https://www.ihe.net/	Profiles (XDS, XCA, CT, etc.); Semantic and technical
EEHRxF	European Electronic Health Record Exchange Format	https://ehr-exchange-format.eu/	Technical

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Standard, Framework, Environment	Name	Link	Additional layer(s) & Notes
CAMSS	Common Assessment Method for Standards and Specifications	https://interoperable-europe.ec.europa.eu/collection/common-assessment-method-standards-and-specifications-camss	Technical
TEHDAS	Towards the European Health Data Space	https://tehdas.eu/	Technical
ISO/IEC 5259 – 1: 2024	Artificial intelligence- Data quality for analytics and machine learning	https://webstore.iec.ch/en/publication/96735	Technical

Table 10. Organisational Interoperability Standards

Semantic Interoperability

Based on the adopted strategy for data preparation, it is essential to determine whether the semantic framework used across primary and secondary use will be homogeneous or whether a mapping mechanism will be required to ensure compatibility and interpretability.

This decision has direct implications for how semantic layers are embedded throughout the data lifecycle:

- At collection, to ensure consistent terminology and coding (e.g., SNOMED CT, LOINC, ICD, ICPC)
- During standardisation, to align metadata, formats and ontologies
- At publication, to support cataloguing and interpretability
- At discovery, to enable semantic search and cohort identification

Semantic interoperability is particularly critical for secondary use, where data must be aggregated and interpreted across domains, institutions and jurisdictions. A shared or mappable semantic layer enables cross-domain analysis, cohort identification and meaningful reuse of data assets.

Recommendations, Resources & Tools

- Apply internationally recognised clinical vocabularies, coding systems and data models such as those included in table 10 below.
    - SNOMED CT: a comprehensive clinical terminology that enables the consistent representation of clinical content in EHRs and research datasets. It supports multilingual implementation and is key for aligning clinical terms across countries.

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- LOINC (Logical Observation Identifiers Names and Codes): standard for identifying laboratory and clinical observations. Widely used in diagnostics, vital signs and laboratory data collection.
- ICD-11 (International Classification of Diseases): the latest WHO disease classification, used for clinical documentation, reporting and epidemiological analysis.
- ICPC-3 (International Classification of Primary Care): the last revision of the global standard developed for coding and organising clinical information in primary care.
- ATC (Anatomical Therapeutic Chemical Classification System): used for the classification of drugs and medicines to standardise pharmacological data collection.
- OMOP CDM (Common Data Model): provides a harmonised structure to transform and store health data from different sources in a consistent way, enabling large-scale analytics and multi-site studies.

- Normalise local terminology using tools aligned with the IHE Terminology Sharing White Paper for primary use and the TEHDAS recommendations for secondary use, enabling semantic consistency across countries and systems. These provide a methodology to enable consistent terminology binding across institutions, countries and regions, promoting shared vocabularies and semantic alignment.
- Align local metadata and data terms with standard models to ensure consistent data structure and interpretation across EHDS systems
- Use persistent identifiers (e.g., DOIs, ORCID) to reference metadata, enabling semantic linkage of datasets and resources.
- Use established domain-specific ontologies and taxonomies to enable precise meaning of data elements across datasets.
- Support cross-dataset integration and analysis from multiple sources by harmonising semantic standards.
- Ensure data is understood in order to be reused. Provide clear semantic definitions and annotations so that data can be reliably interpreted and reused across contexts.

Main standards enabling organisational interoperability in Europe are presented in Table 11 below:

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Standard, Framework, Environment	Name	Link	Additional layer(s) & Notes
OMOP CDM	Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM)	https://ohdsi.github.io/CommonDataModel/	Technical; organisational
DCAT-AP	Data Catalogue Application Profile	https://interoperable-europe.ec.europa.eu/collection/semic-support-centre/dcat-ap	Technical (Discoverability, communication)
SNOMED CT	Systematised Nomenclature of Medicine Clinical Terms	https://www.snomed.org/use-snomed-ct	Technical (syntactic interoperability); Organisational
ICD 10/11	International Classification of Diseases	https://icd.who.int/en/	Technical (syntactic interoperability)
ICPC 2/3	International Classification of Primary Care	https://icpc-3.info/	Technical (syntactic interoperability)
ATC	Anatomical Therapeutic Chemical	https://atcddd.fhi.no/atc_ddd_index/	Technical (syntactic interoperability)
LOINC	Logical Observation Identifiers Names and Codes	https://loinc.org/	Technical (syntactic interoperability)
ISO 13606	Health Informatics Electronic Health Record	http://www.en13606.org/index.html	Technical
ISO 11073	Health informatics Device interoperability	https://www.iso.org/standard/77338.html https://www.iso.org/standard/77339.html	Technical
ISO 23903	Interoperability and integration reference architecture	https://www.iso.org/standard/77337.html	Technical
ISO 22989	Artificial intelligence concepts and terminology	https://www.iso.org/standard/74296.html	Technical

Table 11. Semantic Interoperability Standards

Technical Interoperability

Technical interoperability is also a key interoperability layer in the secondary use of data. This type of interoperability should be implemented:

- At collection - via acquisition systems and structured input interfaces. At collection phase systems should be able to load predefined collection forms from a moderated library resulting in structured input interfaces that are based on consensus items to be collected.

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- During/through standardisation – with APIs, data models, validation pipelines
- At publication - using secure repositories and metadata registries
- In discovery - via protocols and indexing services
- At use - through analytical environments and controlled access platforms

Technical interoperability will thus ensure system-to-system communication, performance and scalability.

The discovery phase benefits from the adoption of standards for catalogues and metadata, enabling users to locate, filter, and assess data resources across domains and jurisdictions. Key elements include:

- Metadata standards (e.g., Dublin Core, DCAT, HL7 FHIR Search)
- Catalogue structures (e.g., FAIR-compliant registries)
- Indexing protocols (e.g., OAI-PMH, RESTful APIs)
- Semantic enrichment (e.g., ontology-based tagging)

These standards enable users to locate, filter and assess data resources across domains and jurisdictions.

Each phase of the data lifecycle also benefits from communication standards to ensure consistent data exchange and messaging. Relevant standards include:

- Transport protocols (e.g., HTTPS, MLLP, MQTT)
- Messaging formats (e.g., HL7 v2/v3, FHIR, CDA)
- Authentication and authorization of a *natural person* (e.g., OAuth2, OpenID Connect)
- Audit and traceability mechanisms

Together, these standards support technical interoperability, ensuring that health data can be exchanged securely, consistently, and reliably across systems, domains, and jurisdictions.

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Recommendations, Resources & Tools

- Use standardised data capture tools and APIs that conform to interoperability standard such as those included in table 11 below and relevant IHE profiles.
  - HL7 FHIR (Fast Healthcare Interoperability Resources): a modern, web-based standard for exchanging healthcare information electronically. It supports granular data elements and is widely used in clinical and research interoperability solutions.
  - ISO/IEC 13606: a standard for EHR communication that defines a dual-model architecture to ensure semantic consistency during health information exchange.
  - OpenEHR contributes to technical interoperability by offering standardised APIs and data representations that allow structured health data to be accessed and integrated across systems.
  - ISO/IEC 11179: a metadata registry standard used to describe, register and share metadata in a harmonised way, ensuring that collected data is annotated with meaningful context.
  - IHE Profiles (e.g., XDS.b, XDS-I, PIX/PDQ, BPPC): interoperability specifications developed by Integrating the Healthcare Enterprise to support standard-based sharing of clinical documents, patient identity management and consent directives.
- Enable integration with local Electronic Health Records/Hospital Information Systems (EHR/HIS) to prevent data silos and duplication.
- Ensure secure transmission of data using protocols like TLS and access control mechanisms (e.g., OAuth2, GA4GH AAI).
- Use structured data entry formats to enable downstream harmonisation.
- Use tools such as REDCap (Research Electronic Data Capture): a secure web application for building and managing online surveys and databases. It supports structured data collection for clinical research and is compatible with data standards like CDISC and FHIR.
- Use FHIR Questionnaire: a FHIR resource that allows structured data entry and supports complex workflows for patient-reported outcomes, clinical forms and surveys.

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- Use data harmonisation tools and standardised metadata schemas (e.g. HL7 CDA) to ensure consistent technical structuring of health data across regions.
- Use open access repositories with version control to maintain interoperable and traceable datasets.
- Leverage AI tools to assist healthcare providers in post-coding free-text clinical data reports, facilitating data integration and analysis
- Support federated search across datasets to allow seamless data discovery.
- Use tools in secure processing environments to conduct data analyses while protecting sensitive data and in compliance with the EHDS requirements.
- Archive publications with persistent identifiers and standardised metadata to ensure reproducible and interoperable referencing across European platforms.

Main standards enabling technical interoperability in Europe are presented in Table 12 below:

Standard, Framework, Environment	Name	Link	Additional layer(s)
HL7 FHIR / HL7 v3	High Level 7 / Fast Healthcare Interoperability Resources	https://hl7.org/fhir/	Semantic (model, architectural); Syntactic interoperability
HL7 v2	High Level 7 version 2	https://www.hl7.org/about/	Syntactic and communication environment; message data format
DICOM	Digital Imaging and Communications in Medicine	https://www.dicomstandard.org/	Semantic; Organisational
IEEE 3652.1	Architectural Framework and Application of Federated Machine Learning	https://www.standards-global.com/wp-content/uploads/pdfs/preview/2183131	Mainly organisational

Table 12. Technical Interoperability Standards

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6. INTEROPERABILITY IN THE PRECISEU MEMBER STATES

Despite interoperability is essential for enabling cross-border projects and collaboration across European Regions, the state of the art is different across countries.

The table below presents the current readiness of different European countries in terms of interoperability. As the European Health Data Space (EHDS) continues to evolve, with secondary use of data expected to be fully operational around 2029, this table should be considered a point-in-time assessment of the situation. Further information detailing the interoperability strengths and challenges per Member State and interoperability layer can be found in the Annex. That information can also be extensively found in Deliverable 4.1 (PRECISEU readiness framework). Adoption of the recommendations contained in this Interoperability Framework will contribute to strengthening interoperability across Member States.

Country	Legal	Operational	Semantic	Technical
Germany	Strong data protection laws; GDPR compliance; legal support for data exchange.	Coordination across federal and state healthcare bodies; standardised workflows in hospitals are variable.	Use of international coding standards (ICD-10, LOINC); partial adoption of HL7/FHIR.	EHR systems interoperable within hospitals ongoing; national infrastructure in place; secure exchange mechanisms developing.
Spain	National legislation supports EHR interoperability; regional regulations broadly aligned.	Some regional implementation autonomy; partial integration across healthcare services.	Standardised coding for diagnoses and laboratories; semantic alignment varies.	Centralised and regional EHR systems; uneven use of HL7/FHIR; secure APIs for data exchange.
Belgium	Legal framework supports cross-border data sharing; GDPR-aligned.	Coordination among multiple communities/regions; regional autonomy in operational management.	ICD-10 used; LOINC, and SNOMED partially implemented.	Multiple hospital information systems connected; FHIR adoption ongoing.
Bulgaria	Legal provisions support health data sharing; national EHR law in place.	Central coordination via Ministry of Health; regional hospitals follow central rules.	Coding standards applied inconsistently; ICD-10 used.	National EHR backbone with connected hospital systems; interoperability improving.
Romania	National eHealth legislation; alignment with GDPR principles.	National coordination with limited regional autonomy.	Use of ICD-10, SNOMED in pilot projects; semantic integration uneven.	Centralised EHR platform; MIS integration varies; FHIR adoption in progress.

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Country	Legal	Operational	Semantic	Technical
Italy	GDPR-aligned legislation; regional autonomy in health policy.	Regional EHR implementation; coordination through national health networks.	ICD-10, LOINC, SNOMED applied variably; terminology management partially standardised.	National infrastructure exists; interoperability across regions is uneven; FHIR partially implemented.
Lithuania	Legislation supports EHR and data sharing; GDPR-aligned.	National eHealth coordination; operational integration with regional facilities.	ICD-10, LOINC applied in major institutions. SNOMED growing	EHR systems interoperable via APIs; secure national data exchange; FHIR adoption ongoing.
Sweden	Strong legal framework for health data; GDPR-aligned.	Regional healthcare systems integrated nationally; operational standards in place.	ICD-10, LOINC, SNOMED widely implemented.	National EHR infrastructure; high interoperability across regions; secure API-based exchange.
Netherlands	GDPR-aligned legislation; legal support for health data sharing.	Centralised coordination with regional hospital autonomy.	ICD-10, SNOMED CT, LOINC applied nationally.	Interoperable EHR systems; use of FHIR for data exchange; secure national health data infrastructure.
Greece	Legal framework supports health data exchange; GDPR-aligned.	National coordination with regional hospital operations; limited interoperability at local level.	ICD-10 and LOINC partially implemented; semantic standards inconsistently adopted.	National EHR backbone under development; partial integration via MIS; FHIR adoption limited.
Ukraine	GDPR-aligned laws in progress; Law on Personal Data Protection and electronic records evolving.	Centralised eHealth governance; regional hospitals have limited autonomy; capacity varies.	ICD-10, ICPC-2, LOINC, DICOM, SNOMED CT in gradual and uneven adoption; inconsistent across facilities.	EHS with Central Component; MIS integration via APIs; patient access via decentralised PIS; FHIR recommended but uneven adoption; pseudonymisation in place.

Table 13. Summary of Interoperability Status per Interoperability Layer and PRECISEU Member State

7. ARTIFICIAL INTELLIGENCE

Artificial intelligence (AI) and natural language model (NLM)/processing (NLP) are increasingly important for advancing semantic interoperability in health data. AI technologies are used to transcode unstructured clinical narratives into standardised codes, facilitating the harmonisation and secondary use of health data. For example, AI-driven tools can extract and map clinical concepts from free-text electronic health records to standard terminologies such as SNOMED CT or LOINC, improving data quality and enabling large-scale analytics. The PRECISEU Framework recognises the potential of AI to enhance data interoperability, while also acknowledging the need for compliance with evolving EU regulations, such as the EU AI Act, and adherence to ethical standards and data protection requirements.

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As previously highlighted, the greatest impact and benefit for secondary use can be achieved when the quantity and quality of data recorded for clinical and care purposes is substantial, and when the models adopted for data capture comply with shared standards.

A strategy to pursue in this area- strongly influenced by the data collection phase of primary use- is to record as much information as possible using standardised formats, through shared coding systems.

Alternatively, or in addition, it is advisable to enable care professionals who produce free-text content to transcode their reports using NLP tools that suggest appropriate codes based on the automated interpretation of their texts.

This approach allows care providers both to verify the quality of the proposed coding and to provide feedback that could help to refine the interpretative model of the AI tool, contributing to a continuous and participatory human-AI improvement process.

In the European Member States and associated countries under or adhered to the EHDS, interoperability is still an ongoing question not only in data, but also in AI. The foundational AI standards, as well as the harmonisation of the big data ecosystem and the AI trustworthiness are still under development, which hinders AI implementation in healthcare and innovation settings across Regions.

Artificial Intelligence in health can only be trustworthy and effective when built on high-quality, interoperable and well-governed data. The interoperability foundations outlined in this deliverable—common standards, semantic harmonisation and secure, FAIR-by-design infrastructures—form the conditions required for compliant and safe AI under the EU AI Act. PRECISEU strengthens this effort by helping regions converge on shared data practices and maturity levels, reducing fragmentation and enabling AI solutions to operate consistently across diverse European ecosystems. Policymakers should therefore prioritise investments and governance measures that reinforce data quality and interoperability in alignment with the EHDS, ensuring that AI-enabled innovation can scale safely, equitably and sustainably across Europe.

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9. ANNEXES

Interoperability strengths and challenges in Member States per Interoperability Layer

The following annex presents a country-by-country overview of interoperability strengths and challenges across the different interoperability layers. It highlights common patterns, gaps and good practices identified across Member States in PRECISEU. The PRECISEU Interoperability Framework recommendations, standards and tools provide evidence to address identified needs, build on existing strengths and incorporates lessons learned to support the implementation of interoperable systems aligned with the European Health Data Space (EHDS).

Interoperability Layer	Germany	
	Strengths	Challenges
Legal	• GDPR compliance with strong anonymisation/pseudonymisation measures. • Citizens have clear rights to access, correct, transfer, and restrict their health data; opt-out available for secondary use.	• EHDS regulation is still under negotiation; unclear which data holders will be included. • Healthcare professionals have persistent concerns about misuse of secondary data.
Organisational	• Federated EHR model supports interoperability between decentralised systems. • National contact point connected to MyHealth@EU facilitates secure cross-border data exchange. • Regional initiatives (e.g., Forum Health Region Baden-Württemberg) provide structured support for data sharing	• Decentralised healthcare system leads to significant regional variation in practices and infrastructure. • Smaller providers often lack funding, IT equipment, and skilled personnel. • Limited culture of data sharing and incentives for improving data quality
Semantic	• ePA and MII initiatives enable structured digital health data management and integration for research purposes	• Many EHR records are unstructured (PDFs, scanned documents, handwritten notes). • Semantic inconsistencies and limited structured hospital data hinder seamless sharing
Technical	• Health Data Lab, MII, and genomic platforms (genomDE, GHGA) support secure integration and secondary data use. • Innovative technologies (QSens, nanodiag BW) improve diagnostics and monitoring	• Highly fragmented systems with widespread paper-based documentation. • Smaller or less-equipped hospitals face difficulties meeting EHDS technical requirements

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Interoperability Layer	Spain	
	Strengths	Challenges
Legal	• Strong privacy and security frameworks (GDPR + LOPDGDD). • Clear national initiatives preparing legislation and strategies for digital health. • Existing high protection standards for personal data	• Lack of effective harmonisation between EHDS requirements and national legislation. • Very strict GDPR interpretation by AEPD creating uncertainty and limiting data sharing. • Lack of a national opt-out mechanism for secondary use. • Insufficient clarification on patient consent processes and future roles of Health Data Access Bodies.
Organisational	• Strong national governance frameworks supporting digital health transformation. • Significant EU and national funding (NextGenEU, PERTE Vanguard Health, €100M for EHDS). • New national units and initiatives improving coordination (e.g., Spanish Data Lake, Digital Health structures).	• Fragmented healthcare system with insufficient coordination across regions. • Limited patient participation in governance and decision-making. • Reluctance among professionals and citizens to share data for secondary purposes. • Regional differences create barriers to unified national governance.
Semantic	• Active work in the use of standards in many regions and research infrastructures. • Strong biobank and research network with harmonised processes. • National commitment to harmonisation through Digital Spain 2026 and the General Secretariat for Digital Health	• Heavy reliance on unstructured free-text data limiting reusability. • Persistent semantic fragmentation across regions and institutions. • Data silos and inconsistent implementation of standards. • Different regions adopting OpenEHR standard
Technical	• Mature and advanced regional EHR systems. • High level of digitalisation and patient digital access nationwide. • Strong security infrastructure and digital identity tools (DNIe, Cl@ve). • Development of national infrastructures such as ENSALUD and the Spanish Data Lake.	• No fully integrated national EHR; regional systems remain disconnected. • Lack of advanced tools for analytics, AI, real-time data, and genomic information. • Insufficient tools for consent management and secondary use. • Need for more robust national computing capacity and cloud infrastructure.

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Interoperability Layer	Belgium	
	Strengths	Challenges
Legal	• Strong GDPR-based framework, reinforced by national laws (Privacy Act, DPA Act) and the 2023 law creating the HDA. • Active legal reviews and feasibility studies to identify EHDS-related bottlenecks.	• Fragmented legal responsibilities across federal and regional levels. • Slow, unclear procedures for data access and anonymisation. • Persistent privacy concerns and lack of clarity around secondary use •
Organisational	• HDA established as national coordinator for secondary use. • Strong supporting institutions (Healthdata.be, NIHDI, FPS Health). • Regional initiatives such as the Flemish health data space study. • Multiple patient-access platforms enabling data access and control	• Significant fragmentation between federal, regional, and institutional systems. • Weak data-sharing culture in the healthcare workforce. • Limited transparency and communication about data reuse
Semantic	• Mandatory EHR use across hospitals and most GPs. • Adoption of FHIR standards underway, with national implementation guides. • Participation in projects like GDI supporting standardised genomic data.	• Multiple EHR systems cause semantic inconsistencies. • Vitalink data often in PDF, not searchable or analytics-ready. • Incomplete datasets due to uneven use across providers
Technical	• Established platforms for secure exchange (e.g., Vitalink). • Digital prescriptions available via eID. • HDA developing data catalogues, access structures, and governance tools.	• Fragmented technical infrastructure across regions and institutions. • Lack of fully interoperable EHR systems nationwide. • Limited advanced analytics and reuse capabilities due to unstructured formats.

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Interoperability Layer	Bulgaria	
	Strengths	Challenges
Legal	• Strong GDPR and Personal Data Protection Act (PDPA) framework with strict safeguards, consent rules, and enforcement. • Legal basis for citizen access and consent management via NHIS. • Ongoing alignment with EU requirements (EHDS, AI Act, MDR).	• No specific legislation for EHRs or interoperability. • Fragmented legal provisions across multiple laws (Health Insurance Law, Electronic Governance Law). • Unclear rules on data retention and anonymisation for research. • Need to establish and operationalise an EHDS-compliant Health Data Access Body.
Organisational	• National E-Health Strategy 2030 sets a unified vision for a national Health Data Space. • VELES Excellence Hub supports regional cooperation and pilot studies. • Active institutional actors (NHIF, National Center for Public Health, Ministry of Health). • Expanding training and capacity-building efforts (CPD, VELES, collaboration with academia).	• Fragmented health information systems and uneven digital capacity. • Limited funding and absence of long-term sustainable financing models. • Varying levels of digital literacy among healthcare professionals. • Need for stronger stakeholder engagement and clearer governance structures.
Semantic	• NHIS adopts international standards (HL7 FHIR, SNOMED CT, DICOM). • Legislative reforms mandate electronic health records across all medical activities. • Increasing standardisation driven by audits, national strategies, and EU alignment.	• Data often incomplete, inconsistent, or fragmented across systems. • Low digital literacy affects correct data entry and maintenance. • Need for stronger protocols and monitoring systems for data quality.
Technical	• National Health Information System with EHRs, e-prescriptions, and digital patient access. • Investments in cloud solutions, high-speed networks, and fibre infrastructure. • Development of a Digital Health Platform integrating users and institutions. • Participation in VELES enabling secure cross-border data exchange.	• Outdated IT systems in many healthcare facilities. • Poor internet connectivity in rural areas. • Complex integration of legacy systems and diverse software. • Need for clearer regulations to support emerging technologies (AI, secure processing).

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Interoperability Layer	Romania	
	Strengths	Challenges
Legal	• GDPR-aligned framework, supported by several national laws (patient rights, healthcare reform, digital health services). • National Strategy for Digitalisation aims to improve data governance, digital identity, cybersecurity, and alignment with EHDS. • Existing laws regulate telemedicine, teleradiology, and quality management	• Fragmented and outdated legal framework for secondary use; restrictive rules for research and unclear provisions (e.g., correction, deletion, portability). • DES (EHR) non-functional; legal ambiguity on data archiving vs deletion. • Lacks clear rules for open data, liability, and compliance for digital tools. • Missing legislation enabling national-level data exchange and reuse
Organisational	• Ongoing creation of new structures: Digitalisation Unit for Health and planned Agency for Digital Health. • Planned National Health Data Observatory (ONDS) to consolidate and analyse national data. • Centralised governance model ensures uniform regulation.	• Fragmented implementation at hospital level; weak interoperability governance. • Independent Agency for Digital Health stalled; unclear operational roles. • Weak stakeholder trust; lack of collaboration and unclear responsibilities. • Hospitals often disconnected from networks due to cyber concerns.
Semantic	• DES uses HL7 standards to support interoperability (in principle). • PACS systems in some hospitals use DICOM for medical imaging. • Emerging interest in integrating genomics, behavioural and environmental data.	• No unified national data standards or nomenclatures. • Parallel, inconsistent data flows across institutions. • Private providers rarely report data to public authorities. • Large amounts of unstructured data; outdated sharing formats (CDs, printed documents, WhatsApp).
Technical	• A national platform exists: PIAS, integrating SIUI, SIPE, CEAS, and the DES. • Government cloud infrastructure and EU-funded projects aim to improve data exchange. • ROGEN project and other initiatives modernise specialised domains like genomic medicine.	• Persistent fragmentation due to heterogeneous legacy systems. • DES currently inaccessible and under reconstruction. • Poor interoperability between hospitals; lack of national exchange infrastructure. • Frequent technical failures, access issues, and reliance on local doctor-provided credentials. • Many hospitals lack secure or modern IT systems; some remain offline for security reasons.

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Interoperability Layer	Italy	
	Strengths	Challenges
Legal	• EDS Decree (31/12/2024) clearly assigns legal responsibilities: Ministry of Health as data controller; AGENAS as operational manager/data processor. • GDPR-aligned national framework, with strict data protection rules and active supervisory authority (Garante). • Clear national deadlines for EHDS readiness (GPs feeding EHR/FSE by 2025; regional adoption by 2026). • Procedures exist for consent waivers in research under GDPR (though rarely used).	• Highly fragmented legal landscape due to regional autonomy and inconsistent implementation across regions. • Legislative restrictions on scientific research stricter than EU GDPR, limiting secondary use. • Lack of an operational HDAB; AGENAS only designated for anonymised data extraction. • No established governance process for involving citizens/patients in EHDS oversight. • No protocol yet defined for secondary-use access to FSE data.
Organisational	• National governance framework defined through EDS Decree with clear roles (Ministry, AGENAS, regions). • Regional examples of advanced implementation (e.g., Emilia-Romagna fully compliant with FSE 2.0). • Training and digital-skills programmes for health professionals supported by PNRR funding. • Strong participation of research and innovation actors, including Technopoles and national R&D programmes.	• National healthcare remains fragmented into regional systems with uneven strategy implementation. • No regional governance mechanisms to coordinate collaboration among local health authorities. • Weak national-level coordination needed for a unified information model. • Low public awareness and varying trust levels hinder uniform adoption of EHR/FSE. • High variation in consent rates and data usage across regions (e.g., Emilia-Romagna vs national average).
Semantic	• National standardisation efforts: HL7-FHIR adoption for EHR/FSE 2.0; HL7 Italy provides national standards. • INI ensures national-level standardised data sharing. • Tools for semantic/syntactic validation developed by AGENAS and AGID. • Recognised need for biobank–health-data interoperability.	• Persistent heterogeneity in data collection and structuring across regions. • Legacy systems and insufficiently trained staff produce poorly structured primary data. • Current FSE still lacks a complete, coherent representation of patient health. • Telemedicine platforms remain fragmented, reducing semantic consistency.
Technical	• Strong national infrastructure: GARR network, INI, ACN for cybersecurity. • Regional infrastructures such as LEPIDA and SOLE enabling data exchange. • High-performance computing resources (e.g., MarghERita, HPC Leonardo). • National guidelines (2015, 2022) and FSE 2.0 architecture standardise interoperability. • Federated national ecosystem (EDS) integrating regional datasets.	• Uneven regional progress and persistent fragmentation of IT systems. • Need to upgrade infrastructures and integrate regional EHRs under a unified NSIS model. • Telemedicine platforms incompatible across regions. • FSE still not providing comprehensive, timely access to health information. • Regional diversity of systems complicates national interoperability.

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Interoperability Layer	Lithuania	
	Strengths	Challenges
Legal	• Full implementation of GDPR with aligned national legislation. • Solid legal basis for personal data protection.	• Further legislation needed to fully support secondary use of health data under EHDS. • No nationally designated Health Data Access Body (HDAB) yet. • Transparency mechanisms required under EHDS not fully implemented.
Organisational	• Centralised governance through Ministry of Health and NHIF. • National EHR use is mandatory for all providers. • Participation in EU projects (biobanking, One Million Genomes).	• EHDS governance integration still incomplete. • Need for stronger national coordination and readiness for EHDS. • Human resource gaps in health IT, data management, and nursing workforce.
Semantic	• Ongoing efforts to improve data standardisation. • Moves toward openEHR and harmonisation with EU standards.	• Data still requires further alignment with EHDS semantic requirements. • Coexistence of multiple parallel digital systems leads to inconsistent standards and inefficiencies
Technical	• Centralised EHR infrastructure (ESPBI IS) mandated for providers. • Significant telemedicine uptake and strong digital infrastructure. • Investments in biobanks, genomics, and digital health innovation.	• ESPBI IS still needs improvement for full interoperability. • Technical integration with MyHealth@EU still under development. • Multiple overlapping hospital systems hinder seamless data exchange.

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Interoperability Layer	Sweden	
	Strengths	Challenges
Legal	• GDPR compliance is high; Patient Data Act provides strong protection. • Active legal work to align Swedish law with EHDS (Patient Data Act, Public Access to Information and Secrecy Act).	• Legislative changes required to enable secondary use of personal data for research and innovation. • EHDS cross-border access frameworks not fully defined. • National legal adjustments remain incomplete; Sweden will be among the last to join myHealth@EU.
Organisational	• E-Health Agency coordinates national interoperability strategy. • SENASH project (2024–2027) establishes national function for health data sharing and secondary use. • National Interoperability Council standardises requirements and harmonises data sharing	• Decentralised healthcare system leads to fragmented governance and regional disparities. • Lack of unified security governance across regions. • Resource and workforce limitations may affect EHDS implementation at regional levels
Semantic	• National registries use standards like ICD-10, ICD-11, and SNOMED CT for primary care. • SENASH and interoperability council initiatives aim to improve standardisation for secondary use.	• Adoption of standards is not yet mandatory. • Legacy data from decades of regional systems require structuring and harmonisation for EHDS. • Regional variation in documentation and metadata limits seamless interoperability.
Technical	• Well-developed national digital infrastructure and mandatory registries. • Active participation in EU technical projects (GDI, EUCAIM, X-eHealth). • SENASH pilots metadata catalogues and data ordering systems to enhance readiness	• Regional data exchange systems need upgrades; some rely on older standards. • Fragmentation of regional EHR systems complicates cross-region and cross-border interoperability. • Capacity to handle complex data requests remains limited in some regions.

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Interoperability Layer	Netherlands	
	Strengths	Challenges
Legal	• GDPR fully implemented; Dutch GDPR Implementation Act (DGIA) tailors EU rules nationally. • WGBO ensures patient rights, access, and control over health data. • Wegiz mandates standardised electronic exchange of key health data. • Dutch Data Protection Authority (AP) actively enforces data protection and compliance	• National EHDS implementation law still needed. • Material Transfer Agreements (MTA) for data sharing unresolved. • Secondary use frameworks require further alignment with EHDS requirements
Organisational	• Ministry of Health, Welfare and Sport (VWS) leads national strategy. • Health-RI provides national infrastructure for research and innovation. • National Contact Point for eHealth (NCPeH-NL) facilitates cross-border health data exchange. • HDAB-NL project developing secure processing environments and national catalogue for secondary use	• Health data access barriers remain under development. • Fragmentation of health information systems hinders seamless data exchange
Semantic	• Nictiz develops and implements semantic standards (SNOMED CT, LOINC, HL7 FHIR). • MedMij framework standardises personal health environments (PGOs) and enables cross-provider data exchange	• EHR systems remain fragmented; full standardisation and interoperability not yet achieved. • Legacy data integration for secondary use still requires harmonisation
Technical	• Active participation in MyHealth@EU pilot, with Dutch hub implemented by CIBG. • HDAB-NL project builds infrastructure for secure secondary data access. • “Once-only principle” applied for citizen data, supporting integrated digital infrastructure. • Telehealth, AI applications, and digital health platforms increasingly adopted	• Foreign health professionals cannot yet access Dutch patient data abroad. • Smaller or under-resourced providers struggle with fragmented systems, paper documentation, and manual data transfer

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Interoperability Layer	Greece	
	Strengths	Challenges
Legal	• GDPR fully implemented via national Law 4624/2019. • Data Protection Officers appointed in public hospitals; Hellenic Data Protection Authority conducts audits. • Patients have guaranteed access rights to their medical data	• Ministry of Health currently restricts access for secondary use. • No national HDAB has been established; decision-making for secondary data use is uncoordinated and opaque. • Advanced legal frameworks for secure, anonymised, or pseudonymised secondary use are underdeveloped
Organisational	• Ministry of Health responsible for governance; intends to appoint relevant authorities. • National Contact Point for eHealth supports cross-border exchange of digital prescriptions and patient summaries. • EU-funded initiatives (H-DAB, smartHEALTH) provide expertise and test-before-invest services	• Fragmented governance and lack of a central authority for secondary data access. • Institutional implementation of privacy and security varies across healthcare organisations. • Ethical review processes are slow, and institutional collaboration for data reuse is limited
Semantic	• Some adoption of ICD-10 standards and DRGs in hospitals. • HL7 and DICOM standards are included in procurement criteria	• Implementation of international standards varies across institutions. • OMOP-CDM adoption for secondary use is limited. • National semantic standards for EHR interoperability and research use are largely absent
Technical	• Platforms like IDIKA and ATLAS provide national EHR and capacity registries. • Digital prescription services and eHealth infrastructure exist. • Research infrastructures such as ELIXIR are accessible for certain domain	• National interoperability framework is incomplete; EU standards like HL7 FHIR are rarely used. • Infrastructure for secure secondary data access, anonymisation, and data federation is underdeveloped. • Procurement processes and centralised platforms limit SME participation and integration of innovative tools

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Interoperability Layer	Ukraine	
	Strengths	Challenges
Legal	• Centralised national legislation and MoH orders unify eHealth governance. • Pseudonymisation and GDPR-aligned provisions enable secure data exchange. • Alignment with EU/EHDS standards supports future cross-border interoperability	• No official Health Data Access Body (HDAB); secondary-use processes unclear. • Regional enforcement of interoperability rules is inconsistent
Organisational	• Central Component (CC) coordinates e-prescriptions, referrals, sick leave, and financing. • MIS vendors integrate with CC via open APIs, enabling connected workflows. • Master Patient Index (MPI) and Centralised Clinical Data Repository (CCDR) standardise patient/clinical data	• Fragmented adoption across hospitals; no national patient portal. • Limited integration for inpatient, laboratory, and imaging data. • Staff training and digital literacy gaps hinder effective data exchange.
Semantic	• ICD-10, ICPC-2, SNOMED CT, LOINC, and DICOM standards implemented. • FHIR recommended for data exchange and used via MIS-CC integration	• HL7 v2 not used; FHIR adoption uneven across providers. • Inconsistent data entry, free-text usage, and duplicates limit interoperability. • Coverage beyond primary care (e.g., hospitals, labs) still incomplete
Technical	• Secure pseudonymised data exchange via CC and MIS APIs. • Authentication and access controls: OAuth 2.0, ABAC, practitioner digital signatures, encryption. • Integration with state registries (Civil Status, Pension Fund, Diia one-way access). • Supports secondary use, research, AI, and analytics	• No multi-factor authentication; fragmented patient access. • Telemedicine and advanced analytics rely on external funding. • Server capacity and scalability may limit data exchange

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