ERN | EuroBloodNet

12th June 2026 - EHA Congress

Boost real world evidence generation

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European Reference Network | Hematological Diseases (ERN EuroBloodNet)

Funded by the European Union

SESSION 1: EU ACTION PLAN FOR RARE DISEASES

PRIORITY ACTION 6: BOOST REAL WORLD EVIDENCE GENERATION

EUROPEAN PRIORITY FOR RARE DISEASES

HLM4RARE WG6: Boost the generation of real-world evidence by ensuring that rare-disease data are high-quality, interoperable, and clinically useful, to accelerate biomarker discovery and support drug development in rare diseases within the EHDS and EU AI Act Regulation

CHALLENGES

- RDs health data remains scattered.
- Divergent legal, ethical, and governance frameworks between Member States.
- Many healthcare systems lack the infrastructure needed to deploy AI tools at scale.
- Trust, transparency and governance of AI remain major concerns.

ERN-EUROBLOODNET RESPONSE

Clinical Trials & Research

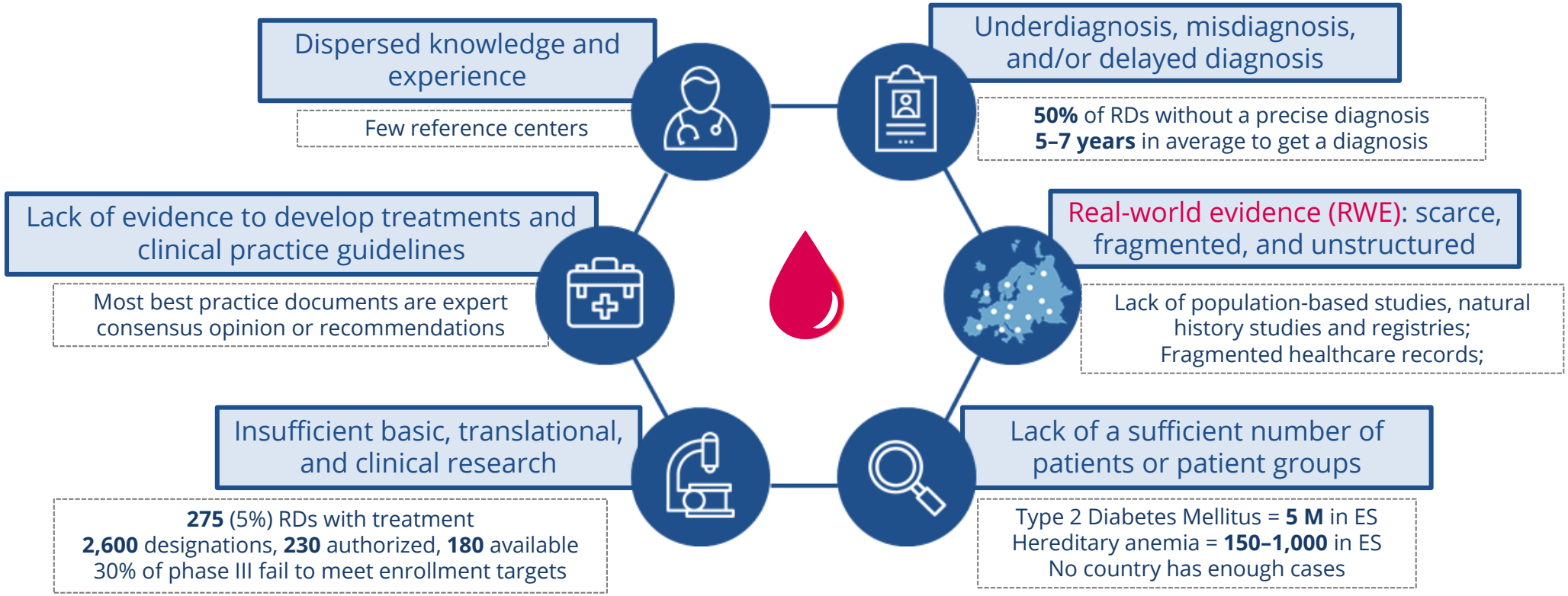
KEY INITIATIVES

ENROL, RADeep, RADiANT, SYNTHEMA, ERDERA

EU ACTION PLAN FOR RARE DISEASES

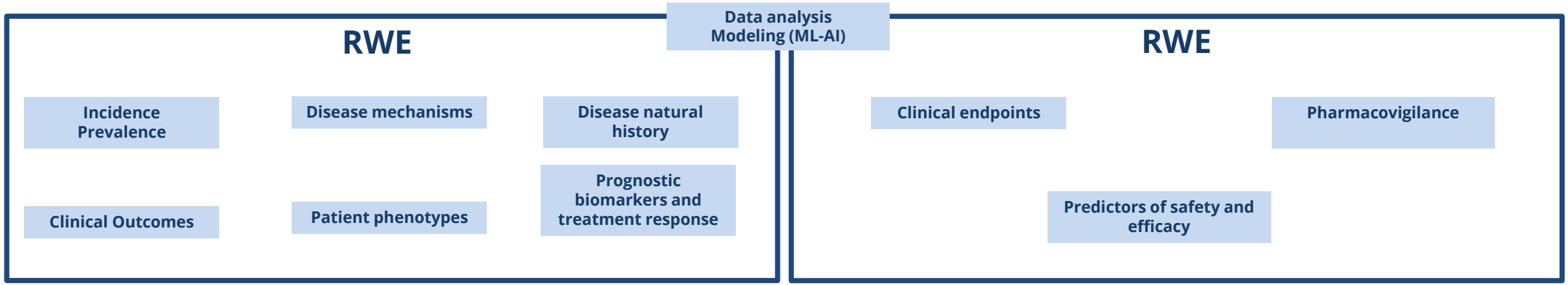
- WG1 Governance & Action Plan
- WG2 Workforce Development
- WG3 Diagnostics & Early treatment
- WG4 Clinical Trials
- WG5 National Infrastructure
- WG6 Real-World Evidence
- WG7 Equitable access to therapies
- WG8 Funding & Sustainability

Unmet needs in Rare Diseases (RDs): +7000 RDs, 30Mi EU



fewer than 15% of paediatric rare-disease patients can account for up to 50% of hospital care processes and costs

Real World Evidence (RWE)



ERN's perspective: main challenges

Rare disease data across the European Union remains fragmented across multiple registries and national systems, limiting its effective use for research, regulatory decision-making, and health system planning.

1 Data repositories and legal framework

- RDs health data are scattered across registries, biobanks, hospitals, research centres and national databases.
- Divergent legal, ethical, and governance frameworks between Member States.

2 Limited interoperability and standards adoption

- Uneven implementation of FAIR principles.
- Limited implementation of RD codification (e.g. Orphacodes), inconsistent adoption of standards, ontologies and common data models (e.g. OMOP)

3 Limited translation from data to clinical value

- Limited quality metrics and assessment of coverage, bias and representativeness
- Limited validation and uptake of AI and data driven tools.

4 Limited integration of RWE

- Lack of systematic approach to integrate real-world data:
- Research Data: x-OMICs, functional data
- Patient self-reported data (PROs, PREs, devices, etc.)

5 Translation into Regulatory

- Registries based RWE is not incorporated into drug regulatory frameworks (PPPs, EMA, HTA).
- Inconsistent participation of patient advocacy groups in design, governance and validation of data and RWE.

POTENTIAL STRATEGIC PRIORITIES (WIP)

1. Establish a European legal and operational framework for regulatory-grade Real-World Evidence generation in rare diseases under the EHDS and the AI Act

2. Rare Disease Codification and EU Data Dashboard based on Standardised Real-World Data

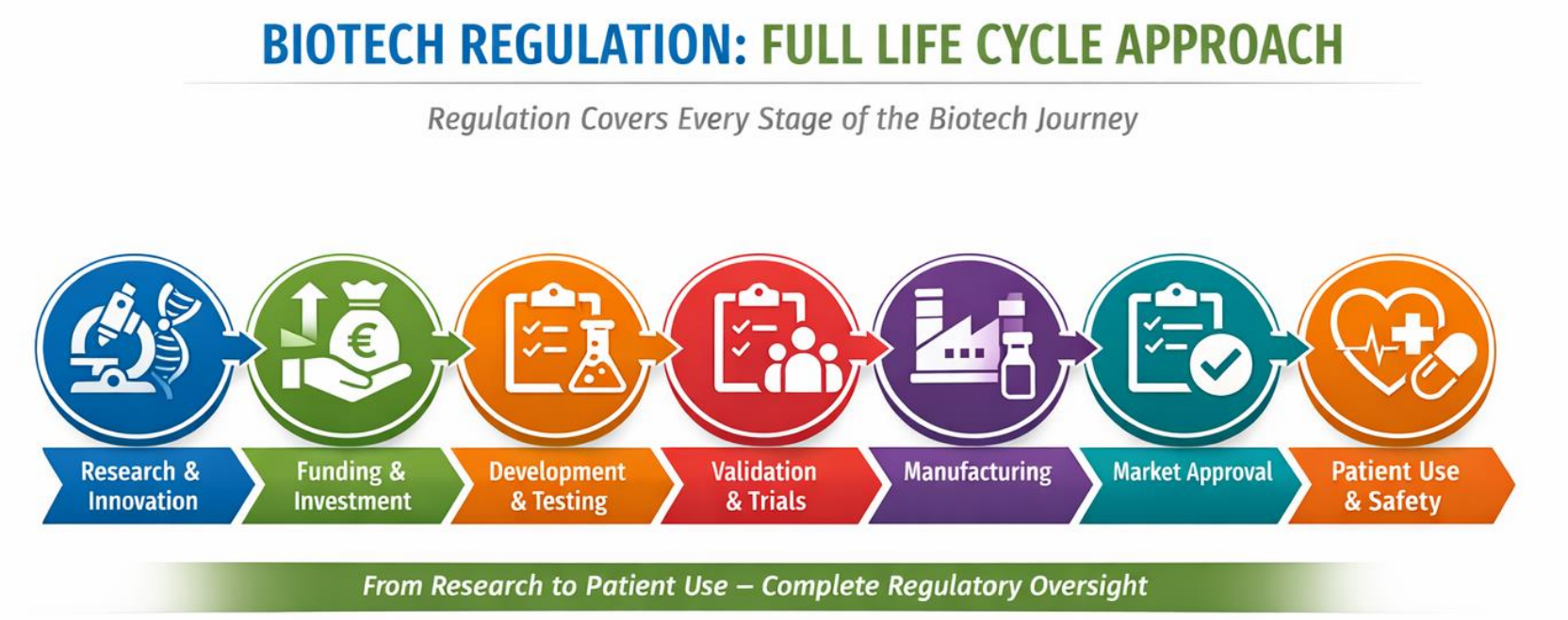
3. EU-RD Data Quality and Utility Framework based on the FAIR principles, the EMA Data Quality Framework, the EHDS, and HTA requirements, incorporating AI-driven methods for data curation, quality assessment, and integration of multi-modal datasets.

4. Boost AI-enabled real-world evidence generation to support comprehensive research, from biomarker discovery and drug development to post-authorisation and post-marketing evaluation, leveraging registries, natural history studies, and federated real-world data infrastructures.

BIOTECH ACT

Global objective

Strengthen Europe’s biotechnology and biomanufacturing ecosystem across the full life cycle, from research and investment to patient use — accelerating innovation, competitiveness and safe translation into healthcare.



Main challenges

Regulatory fragmentation, slow research-to-market translation, limited scale-up capacity, complex evidence and access pathways, fragmented high-quality health data, and the need for trustworthy AI and patient safety.

Main impact

Positions AI, real-world data and regulatory-grade evidence as strategic enablers. For rare diseases, it may reinforce ERN-generated data, evidence generation, clinical development, HTA and patient access.

Regulatory status: currently a legislative proposal; final provisions may evolve through the ordinary EU legislative process.

BIOTECH ACT

Article 31 Guidance on the deployment and use of systems based on advanced technologies, including AI, in the lifecycle of medicinal products

Article 32 Biotechnology testing environments for advanced biotechnology innovations

Article 33 Biotechnology data quality accelerator

Projects

(a) aim to foster the development and deployment of trustworthy and competitive AI systems in health biotechnologies, including large-scale and generalpurpose models relevant for biological, biomedical or biomanufacturing use cases;
(b) assist entities that lawfully hold relevant data and, as regards health data, holders as defined in Article 2(2), point (t), of Regulation (EU) 2025/327 EN 97 ('health data holders') to improve data quality, standardize and make other improvements to such data as referred to in paragraph 1 of this Article;
(c) contribute to the development of Union standards and quality frameworks for data representativeness, provenance, interoperability and annotation in biotechnology;
(d) give due consideration to the interoperability with platforms deployed pursuant to the European Health Data Space (EHDS) and other relevant data spaces;
(e) be aligned with and complement Union initiatives such as the Data Union Strategy, including data labs and AI factories, while addressing the specific requirements of biotechnology datasets, including biological metadata, scientific taxonomies, experimental traceability and regulatory-grade data quality.

ERN's perspective: opportunities to accelarate research through RWE

EUROPEAN RARE DISEASES RESEARCH ALLIANCE

European Commission JOINT RESEARCH CENTRE

EU RD Platform

VIRTUAL PLATFORM
3 levels of access from directory to federation

ERDRI
The European Rare Disease Registry Infrastructure

- European Directory of Registries
- Central Metadata Repository
- Pseudonymization tool

orphanet

FAIR principles

Aggregated data is shared

EMA EUROPEAN MEDICINES AGENCY

Industry partnership

ERNs Research collaborative projects

EUROPEAN RARE DISEASES RESEARCH ALLIANCE

Real World Data
- Leverage primary and population-based data for rare disease outcome research
- Integrate patient cohorts and develop regulatory-grade natural history data resources
- Model disease progression, identify prognostic biomarkers, and enable clinical trial simulation

Clinical Outcome Assessment
- Develop and implement patient-centered COA/PROMs tools
- Assess the socioeconomic impact of RDs

Realise D
compRehensive mEthodological and operational Approach to cLinical trialS in ultra-rarE Diseases

- Development of an efficient patient enrolment system
- New methodologies for clinical trials
- Generation of synthetic data cohorts

EURORDIS RARE DISEASES EUROPE

enrol European Rare Blood Disorders Platform

EMA EUROPEAN MEDICINES AGENCY

EMA Quality Frame
EHDS Data quality and utility label

- Epidemiological & disease burden surveillance
- Promotion of best practices & health planning
- Identification of trial cohorts for Clinical trials
- **Promote research and innovative therapies**

Pseudonymised data is shared

DATA PROVIDERS

INDIVIDUAL CENTRES

EUROPEAN REGISTRIES
NATIONAL REGISTRIES/ NETWORKS

JARDIN

Member States

- Common Data Elements
- EHR extraction, data ETLs, interoperability

CLINICAL OUTCOME RESEARCH PLATFORM

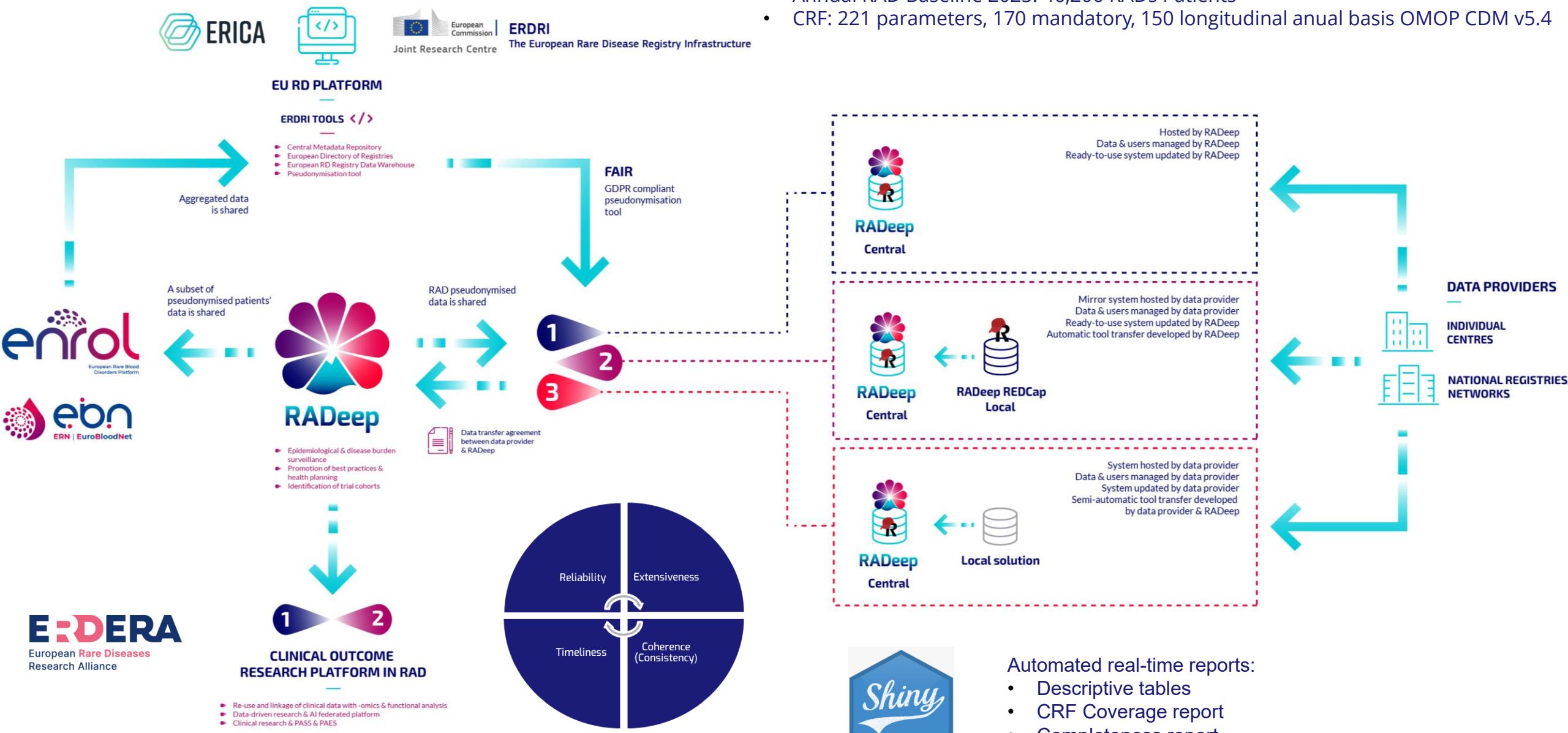
- Re-use and linkage of clinical data with -omics & functional analysis
- Data-driven research & AI federated platform
- Clinical research & PASS & PAES

SYNTHEMA

RADeep Ecosystem

Public dashboard: https://www.radeepnetwork.eu/epidemiological-data

- PID: 6631 Patients; 4393 SCD, 107 sites, in 10 countries + 4
- Annual RAD Baseline 2025: 46,206 RADs Patients
- CRF: 221 parameters, 170 mandatory, 150 longitudinal anual basis OMOP CDM v5.4



Automated real-time reports:

- Descriptive tables
- CRF Coverage report
- Completeness report

RADeep - RADiANT

ERN- EuroBloodNet
Rare Anemia Disorders registry

GDPR / EHDS

Federated platform registry

GDPR / EHDS / Drug and MD Regulations / AI Act

Federated platform: 4 nodes in 4 countries

11 Ongoing collaboration agreements involving 180 (117 active) HCPs in 10 EU countries:
12 Member States

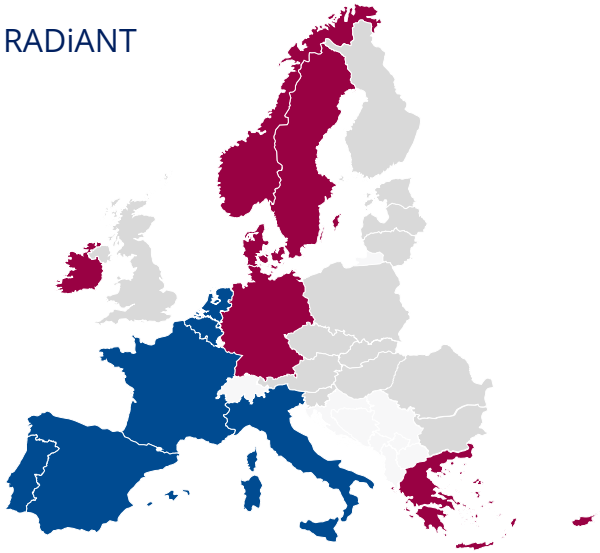
- Belgium
- Cyprus
- Denmark
- France (2)
- Greece
- Italy
- Portugal
- Spain
- The Netherlands
- + Norway

- *4 in negotiation*
- *France*
- *Ireland*
- *Sweden*
- *Switzerland*

Countries onboard in RADiANT
4 EU countries

- France
- Italy
- Spain
- The Netherlands

2 in negotiation
- *Belgium*
- *Portugal*



1,289 enrolled Sickle Cell Disease patients across Europe

Netherlands (SCORE, 4 sites)
487 patients (45% PED)
Deployment
Virtual Machine
Connected to Central Node

Spain (INTEGRA, 10 sites)
334 patients (76% PED)
Deployment
Virtual Machine
Connected to Central Node

RADiANT
Central Node
Federated AI
Data Harmonisation
Secure Computation

Italy (1 site)
130 patients (75% PED)
Deployment
Virtual Machine
Connected to Central Node

France (2 sites)
494 patients (81.6% PED)
Deployment
Virtual Machine
Connected to Central Node

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Equitable Access to Diagnostics and Early Treatment

Speaker: Prof. Dr. David-Zacharie Issom

A patient-researcher perspective on sickle cell disease & health equity

PERSPECTIVE

Equity in haematology is engineered, not inherited

The science to keep people with sickle cell disease alive and well exists today.

The decisive variable is the system that delivers it:

where you are born determines whether that science reaches you.

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INEQUALITIES BETWEEN COUNTRIES AND SYSTEMS

A burden concentrated where resources are scarce

>515'000
new births with SCD each year

>25 M
people living with SCD worldwide

>376'000
annual deaths, ~11x recorded cause-specific

~95%
of patients live in low- and middle-income countries

The delivery gradient. Disease burden concentrates in sub-Saharan Africa, India, and the Caribbean. Clinical trials, specialist workforce, and funding concentrate in North America, Europe, and the Middle East. The map of need and the map of resources point in opposite directions.

GBD 2021 Sickle Cell Disease Collaborators, Lancet Haematol 2023;10:e585-99. Piel et al., Lancet Haematology Commission, 2023.

CHALLENGES IN DIAGNOSIS

Newborn screening is the first fault line

A drop of blood at birth changes a life trajectory. Universal newborn screening enrols infants into protective care before the first crisis. Its presence or absence draws the sharpest line between systems.

Systems with universal screening

Programs established in the USA, UK, France, the Netherlands, and parts of Spain

Diagnosis precedes symptoms; prevention starts in infancy

Childhood survival exceeds 95% within structured care

Systems without universal screening

Switzerland has no SCD in its national screening panel

Diagnosis often follows a severe first event: sepsis, splenic sequestration, or stroke

In high-burden low-resource settings, as many as 50-90% of children die before age 5

WHO; Piel et al., Lancet Haematology Commission, 2023. Swiss national newborn-screening panel composition.

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THE IMPORTANCE OF EARLY DIAGNOSIS

Early diagnosis unlocks a chain of prevention

Each intervention below works only when the child is already known to the system.

→ Diagnosis is the gate that opens all of them.

1	**Penicillin prophylaxis**	From a few months of age, preventing pneumococcal sepsis, a leading early cause of death.
2	**Vaccination**	Pneumococcal, Hib, and meningococcal schedules reduce invasive infection.
3	**Transcranial Doppler**	Screening from age 2 identifies stroke risk; chronic transfusion then reduces first stroke by > 90%.
4	**Hydroxyurea**	Raises fetal haemoglobin, reducing VOCs, acute chest syndrome, transfusions, and mortality.

STOP trial (stroke risk reduction). Piel et al., Lancet Haematology Commission, 2023.

ACCESS TO CARE: BLOOD PRODUCTS

Safe transfusion depends on donor diversity

Transfusion is a backbone therapy for VOCs & stroke prevention, acute chest syndrome, and spleen sequestration.

Transfusion safety depends on matching red-cell antigens, and matching depends on who donates.

Ancestry mismatch

Patients are largely of African, Caribbean, and Mediterranean ancestry; European donor pools are largely of European ancestry, creating Rh, Kell, and Duffy antigen differences.

Alloimmunisation

Without extended matching, antibody formation rises steeply, causing **delayed haemolytic reactions and hard-to-source future units.**

The equity lever

Diverse donor recruitment, red-cell genotyping, extended Rh and Kell matching, and rare-donor registries restore safe supply.

Swiss and European reality. Blood systems built around majority-ancestry donors **meet equity by diversifying the donor base and adopting genotype-guided matching.**

Chronically transfused SCD: alloimmunisation reduced substantially by extended antigen matching.

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UNMET NEEDS: THE INNOVATION GRADIENT

New therapies risk widening the gap

The therapeutic ladder has grown quickly. **Without deliberate access design, each new drug lifts a few and leaves the majority further behind.**

Gene therapy. Potentially Curative; list prices around 2-3M USD per patient

Stem-cell transplantation. Curative, requires a matched donor and transplant units

Chronic transfusion. Effective, dependent on safe matched blood supply; iron overload; alloimmunisation; delayed reactions; infections

Hydroxyurea. Low-cost oral therapy; the global equity baseline; many don’t see adequate response; side effects

A steep cliff of logistical hurdles

Curative therapies need erythrocytaphereses, conditioning, and transplant infrastructure that 95% of patients cannot reach. Access frameworks would turn a breakthrough into a benefit.

Casgevy and Lyfgenia approvals 2023-2024 (US, UK, EU). Piel et al., Lancet Haematology Commission, 2023.

A SWISS PERSPECTIVE

Wealth alone does not deliver equity

A high-income system with excellent tertiary care still carries the same structural fault lines.

Each one is a clear, achievable lever.

Newborn screening

Add SCD to the national screening panel to enrol infants before the first crisis.

National registry

Consolidate an interoperable registry to drive surveillance, planning, and equitable resourcing.

Diverse blood supply

Grow a donor base that mirrors the patient population and adopt genotype-guided matching.

Coordinated continuum of care pathways

Formalise nurse-led care and include mental health support across the lifespan and the paediatric-to-adult transition.

Care concentrated in HUG, CHUV, Zurich, and Bern. Echoes the ERN-EuroBloodNet EU landscape (Manu Pereira et al., 2023).

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AI & Synthetic Data Generation

Speaker: MATTEO DELLA PORTA

Increased access to healthcare data is needed to accelerate the generation of clinical evidence in hematology

97%

of healtcare data remains unused

Source: Deloitte, Health Data, 2023

Main reasons:

- Privacy limitations (GDPR)
- Lack of data harmonization from different sources
- Data are not structured and are dispersed

EU - funded Projects

GENOMED4ALL

SYNTHEMA

Realise D

compRehensive mEthodological and operational Approach to cLinical trIalS in ultra-rarE Diseases

synthia

Synthetic Data to accelerate research in Hematology

- **Synthetic data** are artificial data generated by an algorithm trained to learn all the essential characteristics of a real dataset. The new data are neither a copy nor a representation of the real data. Since they are not real data, they are not regulated by particular limitations so they can be easily accessed and shared.

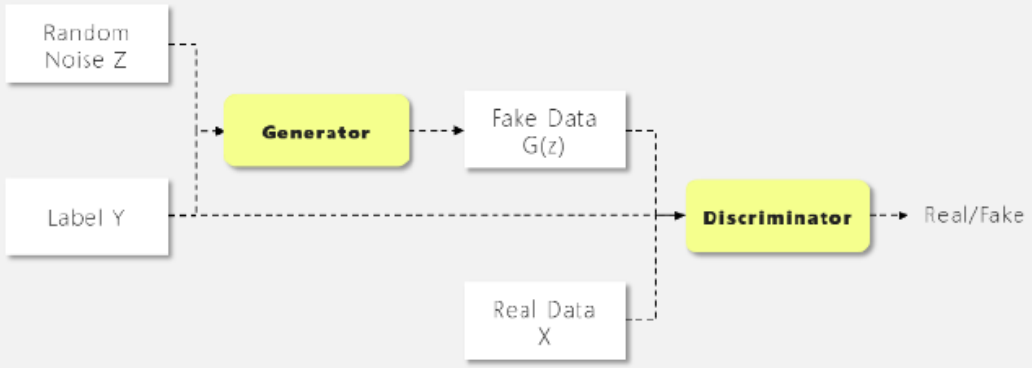


Figure 2 Conditional Generative Adversarial Networks architecture

Properties and possible applications

- Data sharing (Privacy/GDPR)
- Classes balance and resolution of missing information (Data harmonization)
- Data augmentation
- Algorithms training and validation
- Generation of new evidence

Chen R et al. Nature Biomedical Engineering 2021;5:493–497; Savage N et al. Nature 2023 doi: 10.1038/d41586-023-01445-8

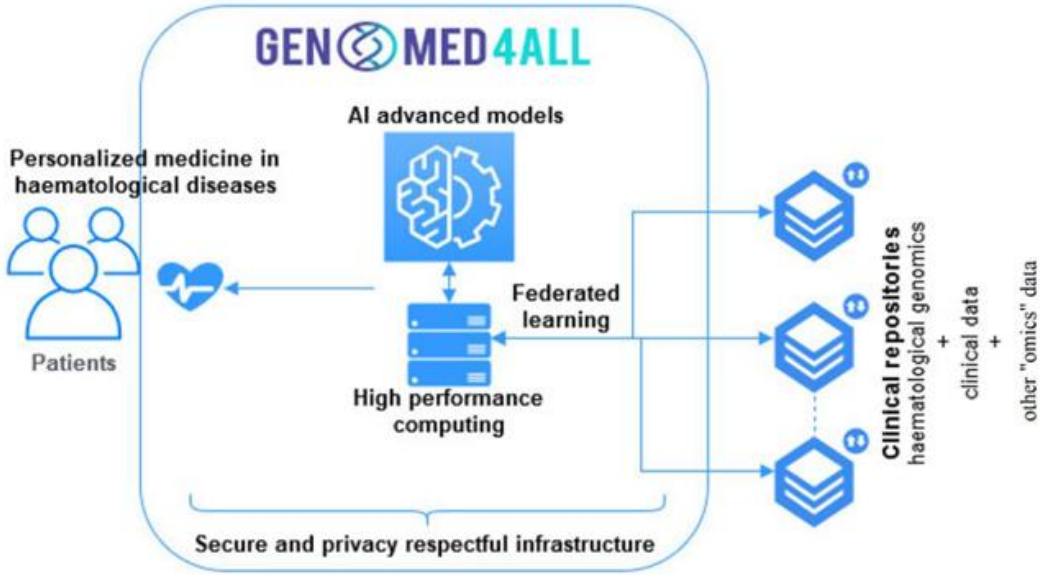
Synthetic data and next-generation clinical trials in hematology

Phase II study of anti-GD2 Chimeric Antigen Receptor-Expressing T cells (GD2-CART01) in pediatric patients affected by relapsed/progressing Neuroblastoma

Prof F Locatelli – Dr.ssa F Del Bufalo

Funded by the European Union

Federated Learning to support Personalized Medicine in Hematology



Federated Learning by AI

- Innovative technologies for data collection and analysis to preserve data privacy are required for implementing personalized medicine
- Federated learning addresses privacy concerns by collaboratively training algorithms without sharing data.

Alvarez F et al, Lancet Digital Health, under revision

The PATHroclus project for Digital Pathology

Specific project's aims:

1) Deploy the *PATHroclus* federated platform
2) Utilize innovative AI algorithms to create next-generation diagnostic and prognostic tools
3) Develop a comprehensive database integrating digital pathology, clinical and genomic information to design next-generation classifications for myeloid and lymphoid malignancies
4) Develop a virtual atlas for hematological malignancies as an educational resource to improve diagnostic standards and reproducibility across Europe

Consortium:

- *M Della Porta - Humanitas*
- *P Harrington – King's UK*
- *A Turki – Essen DE*
- *JM Middeke – Dresden DE*
- *A Mosquera Orgueira - ES*
- *José Cardia – Lisbon PT*
- *M Ponzoni – OSR, IT*

Della Porta M – EHA innovation Grant 2025

THANK YOU!

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WORK IN PROGRESS

1 European framework for regulatory-grade RWE

Legal, ethical, operational and digital foundations for cross-border rare disease data use

1.1 ERN Legal & IT network

Transversal ERN subnetwork to adopt EU data governance templates for secondary use of rare disease data.

1.2 Patient-centred research

Patient organisations embedded in data plans, study design, results review and return of findings.

1.3 ERN-validated digital platform For RD RWE

Interoperable templates, workflows, AI-assisted completion, dynamic consent and transparent data-use tracking.

Governance → Trust → Reuse

1.4 Central national ethics approval

National centralized ethics routes for registries and natural history studies to reduce duplication.

1.5 EU legislative framework interanalysis

Practical alignment of GDPR, EHDS and AI Act for RWD research, regulatory use and AI deployment.

1.6 Dedicated resources for RWE Generation in healthcare providers

Funding and capacity for data stewards, IT specialists and research coordinators in ERN clinical units.

ENROL Data Transfer from RADeep

Country	Nº of patients
Belgium	1,161
Cyprus	406
Denmark	130
France	917
Greece	268
Italy	1,881
Spain	1,155
The Netherlands	518
Norway	90
Portugal	105
Total	**6,631**

Data by 15/05/2026

European Rare Blood Disorders Platform – ENROL Registry

Endorsed by the **European Hematology Association (EHA), ENROL is the central registry of the ERN-EuroBloodNet, covering** both new and already existing registries on rare hematological disorders (RHD).

Aims to **avoid fragmentation** of data by promoting the standards for patients registries' interoperability in line with the **EU-RD-Platform.**

ENROL's principle is to **maximize public benefit from data on RHD** with the only restriction needed to guarantee patient rights and confidentiality, in agreement with EU regulations for cross-border sharing of personal data.

- **Identify unmet needs in RHDs**
- **Share and pool data, reach critical numbers**
- **Analyse KPIs, perform clinical trials & research projects**
- **Knowledge and Evidence generation**
- **better healthcare for RHDs patients**

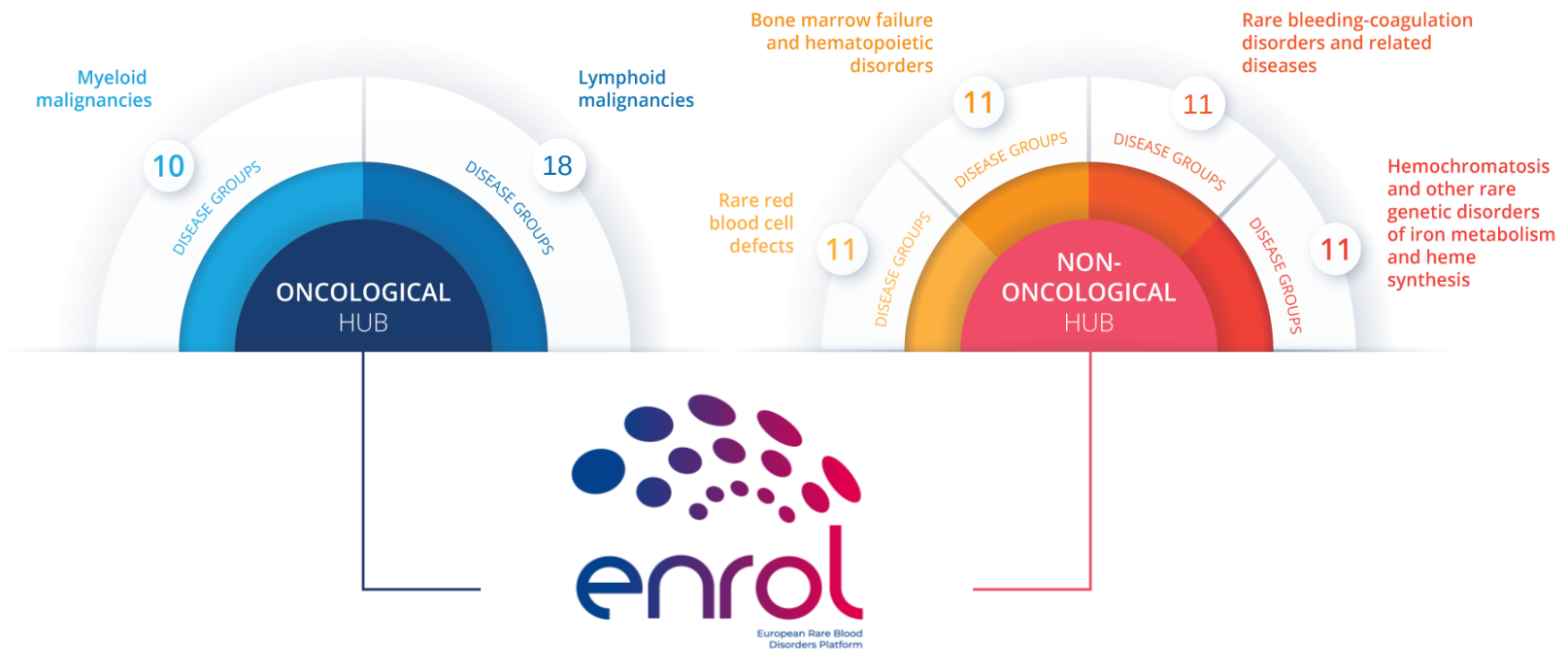
European Rare Blood Disorders Platform - ENROL

Facilitate epidemiological surveillance

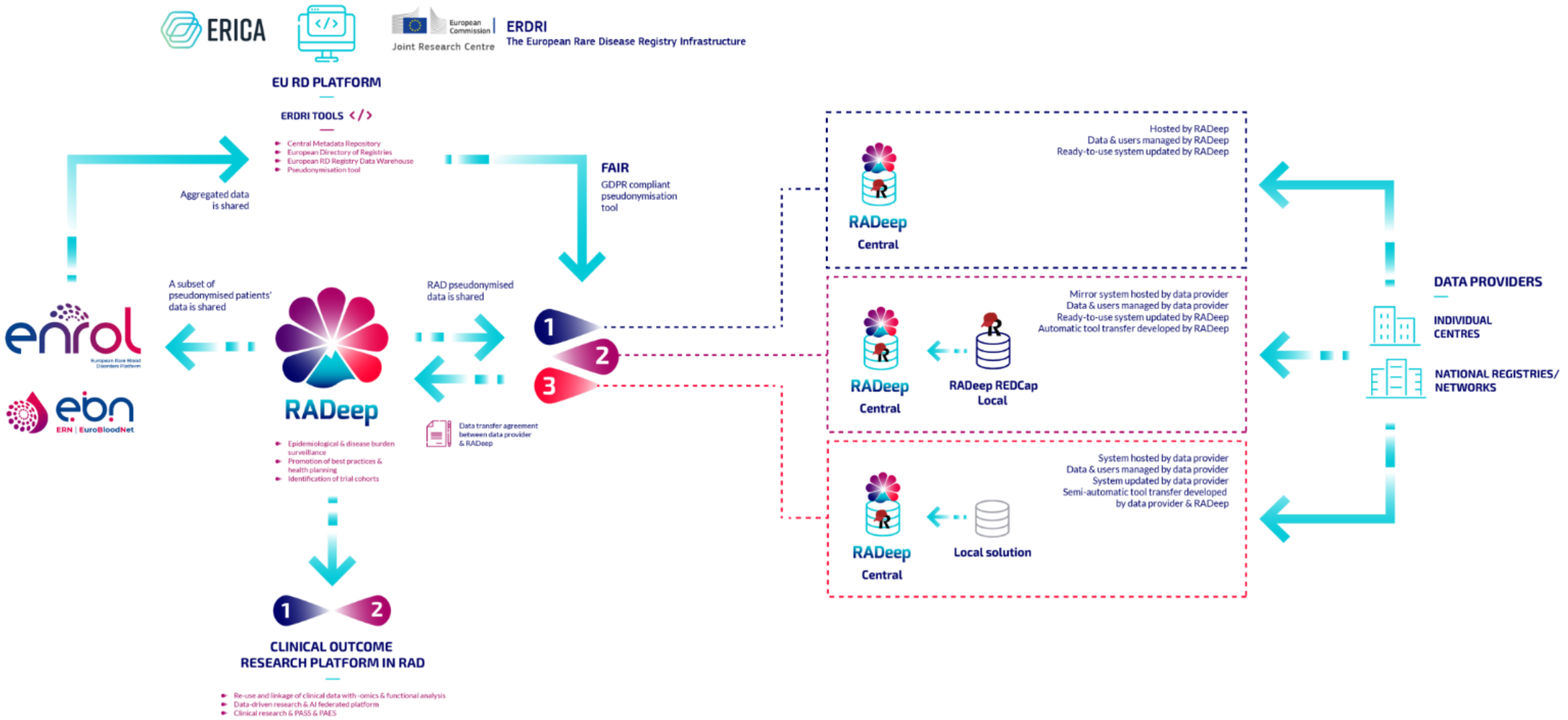
Enhance health planning

Enable the identification of patients' cohorts

Promote research & innovative therapies

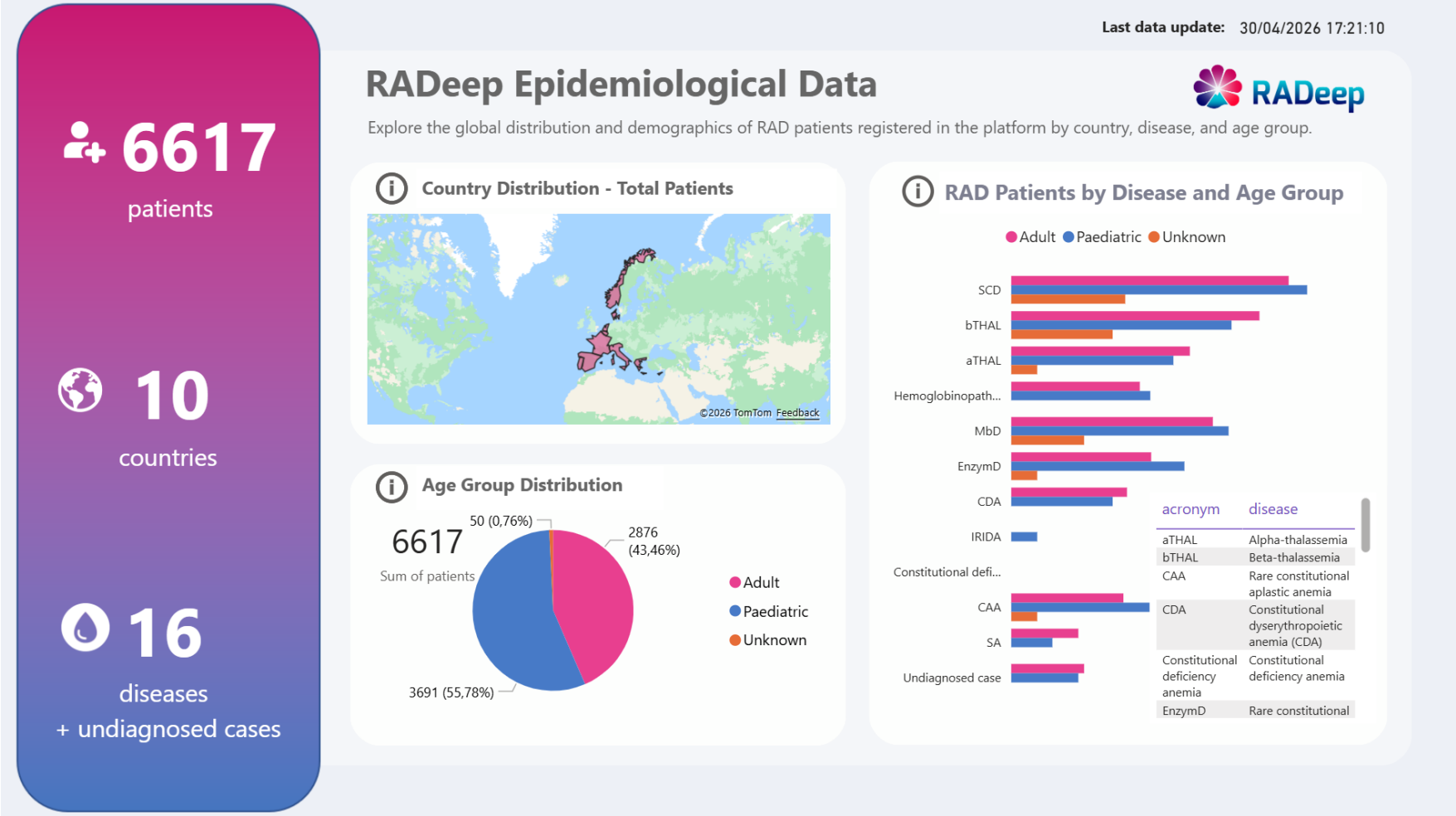


SCD - Strategy for data collection: RADeep



Data quality management

Public dashboard: Epidemiological data | Radeep



European Medicines Agency (EMA) Data Quality Framework (DQF) for RWE generation

Four maturity levels describing the natural evolution of how an organization manages, controls, and improves the quality of its data:

Level 1 — Documented

- This constitutes the **minimum baseline**. Organizations collect essential documentation, including data dictionaries, operational processes, variable definitions, data capture flows, and data transformations.

Level 2 — Formalized / Standardized

- Standardized procedures
- Harmonized validation rules
- Common data models
- Clearly defined roles

This level creates **structural consistency** within the system, enabling reproducibility and comparability across centers or countries.

Level 3 — Automated

Once processes are standardized, they can be **automated**:

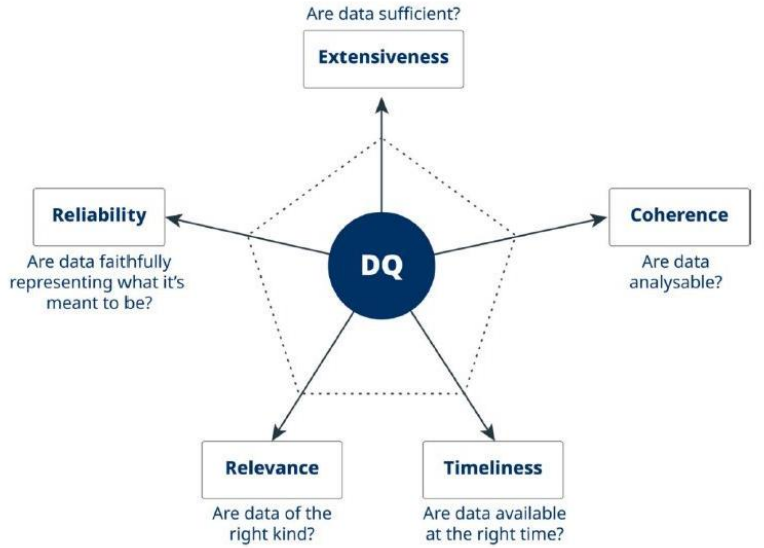
- Automated data validations
- Real-time detection of inconsistencies
- Automatic updating of dashboards
- Replicable ETL workflows
- Automatically generated quality alerts

Automation is **only possible** if the previous steps exist and are robust. This level enables scalability, ensures **continuous quality, and reduces human-driven variability**.

Level 4 — Continuous Feedback

- Continuous improvement systems
- Intelligent alerts
- System learning (identifying recurring errors and points of failure across centers)
- Cyclical quality review
- Indicator-based governance
- Recurring audit mechanisms

While Level 3 automates, Level **4 learns, evaluates, and corrects**. It builds on the automated ecosystem of Level 3 and closes the data quality loop.



EHDS Article 78: data quality and utility label

1. Datasets made available through health data access bodies may obtain from health data holders a Union label relating to data quality and utility.
2. Datasets containing **electronic health data collected and processed with the support of national or Union public funding shall have a data quality and utility label** covering the elements referred to in paragraph 3.
3. The data quality and utility label shall cover the following elements, where applicable:

   a) **for data documentation:** metadata, supporting documentation, the data dictionary, the format and standards used, the source of the data and, where applicable, the data model;

   b) **for technical data quality assessment:** completeness, uniqueness, accuracy, validity, timeliness and consistency of the data;

   c) **for data quality management processes:** the level of maturity of data quality management processes, including review and audit processes and bias assessment;

   d) **for coverage assessment**: the time period, population coverage and, where applicable, the representativeness of the population included in the sample, and the average time frame during which a natural person appears in a dataset;

   e) **for access and provision information:** the time elapsed between the collection of electronic health data and their inclusion in the dataset, and the time limit for providing the electronic health data following the issuance of a data permit or the approval of a data access request;

   f) **for information on data modifications:** the combination and integration of data into an existing dataset, including links with other datasets.

Synthetic data generation in Rare Hematological Diseases

- **Synthetic cohorts for better stratification**

Create synthetic longitudinal datasets combining EHR, genomic, and omics data to improve AML and SCD sub groups classification, identify rare patient subgroups, and enable AI-driven phenotype–genotype matching.

- **Synthetic data for biomarker and endpoint discovery**

Integrate synthetic clinical and omics data to identify prognostic biomarkers, predict disease progression, and develop better clinical endpoints for precision hematology.

- **Synthetic external control arms for faster clinical trials**

Use synthetic patient populations generated based on real-world data from registries as external control arms to optimize recruitment, simulate trials, and accelerate evaluation of new AML and SCD therapies.

- **Synthetic data augmentation to improve quality and reduce bias**

Apply generative AI to address missing or imbalanced data, improve dataset representativeness, and support patient-centered and regulatory-grade real-world evidence analyses.