RADeep

Experience from registries

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EMA workshop on the challenges in drug development, regulation and clinical practice in hemoglobinopathies
July 1st, 2024

Conflict of Interest Disclosure

- Research Grants:
  - Novartis AG
  - Agios Pharmaceuticals Inc
  - Bristol Myers Squibb

- Advisory Board:
  - Agios Pharmaceuticals Inc

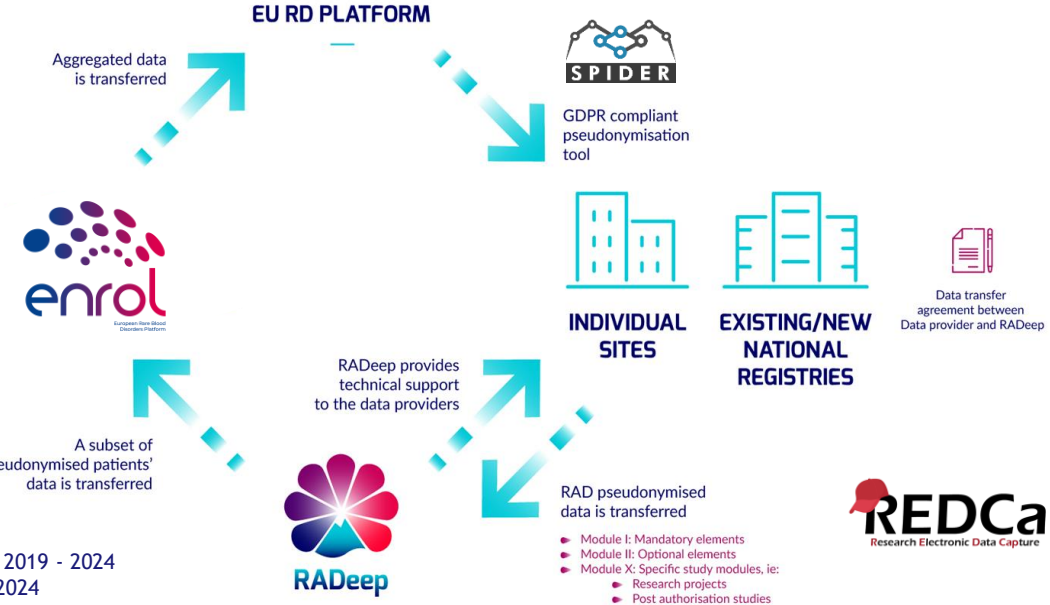
Rare Anaemia Disorders European Epidemiological Platform

- RADeep initiated its activity in 2018 as the EU Patients' Registry on rare anemia disorders (RADs)

www.radeepnetwork.eu

ERICA
European Rare Disease Research Coordination and Support Action

EUROPEAN JOINT PROGRAMME RARE DISEASES



- **Link**
- **Upgrade**
- **Built**

REDCap
Research Electronic Data Capture

ern EuroBloodNet
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Research Grants
Agios Pharmaceuticals Inc, PKD 2019 - 2024
Novartis AG, SCD 2021-2024
Bristol Myers Squibb, THAL 2022-2024

Rare Anaemia Disorders European Epidemiological Platform

- To enable epidemiological and health burden surveillance of RADs in the EU to improve healthcare planning
- To enable translational and clinical research by collecting enough amount of high quality real world data to generate real world evidence for identification of reliable biomarkers for:
  - Disease progression
  - Prognosis
  - Response to treatments

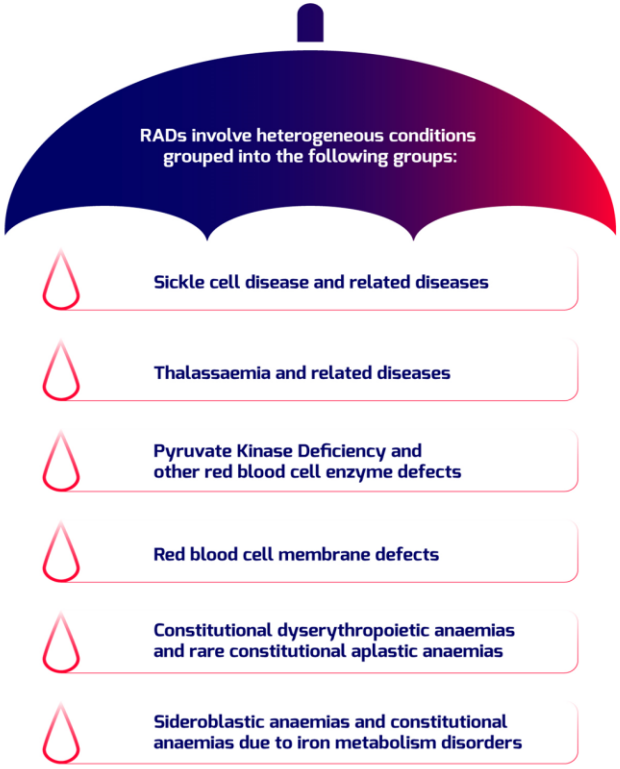
possibility to share and pool data

reach critical numbers

perform clinical trials, research projects

knowledge generation (evidence)

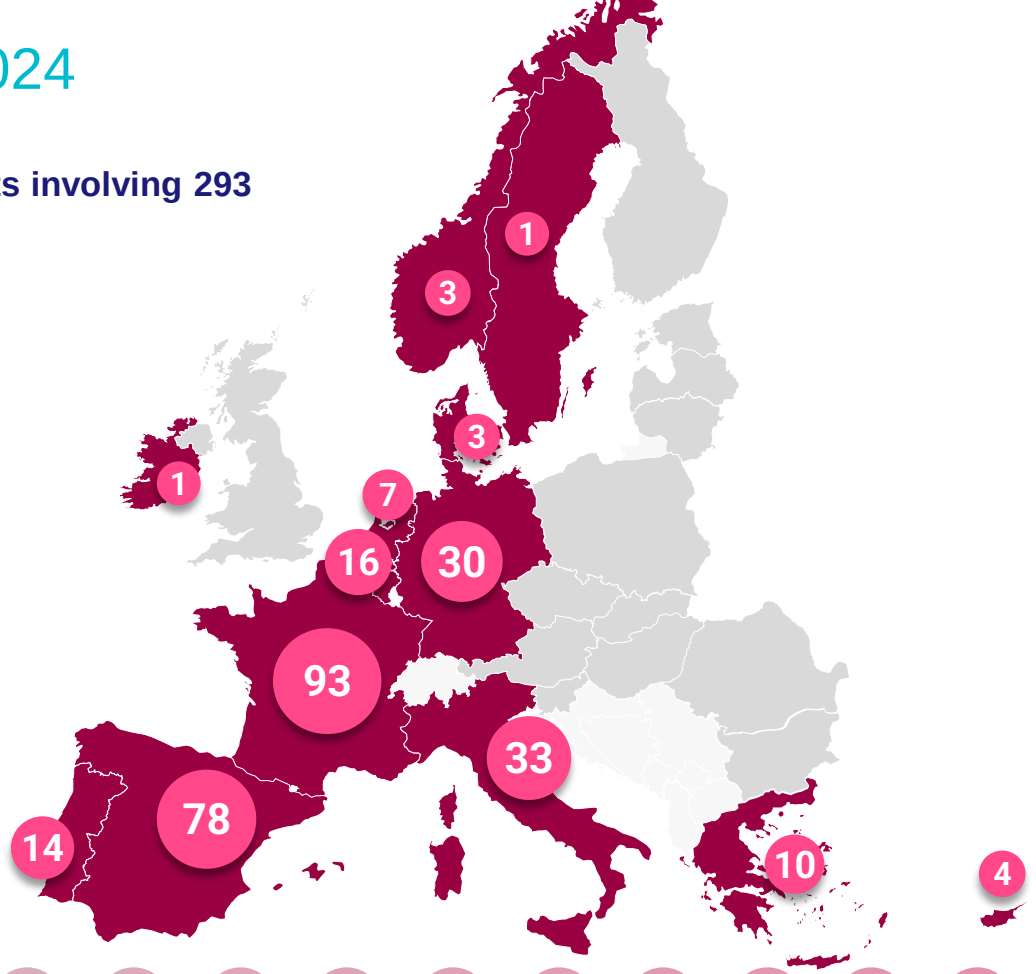
better healthcare for RADs patients



Status of collaborations - 2024

- **15 Ongoing collaboration agreements involving 293 HCPs in 13 EU countries:**

  12 Member States
  - Belgium
  - Cyprus
  - Denmark
  - France (3)
  - Germany
  - Greece
  - Ireland
  - Italy
  - Portugal
  - Spain
  - Sweden
  - The Netherlands
  - + Norway

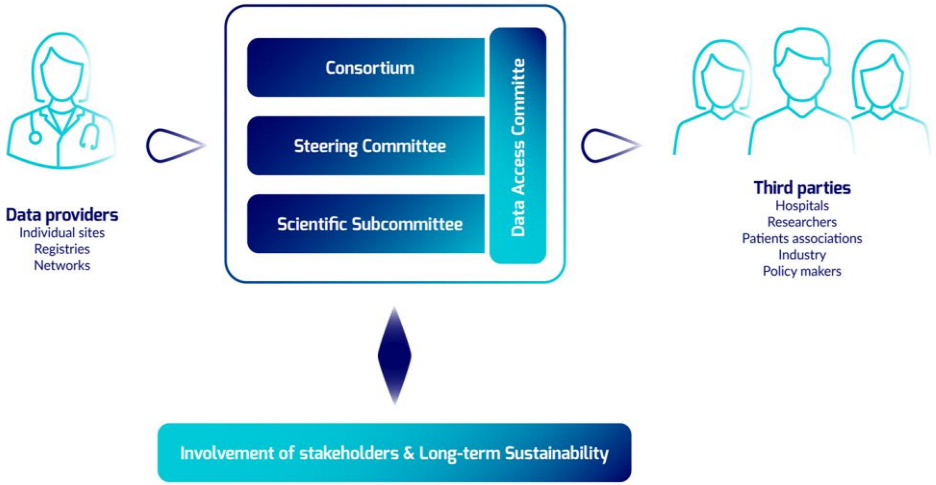


Status of collaborations – 2024 = Patient Individual Data

Country	Main Institution / Registry	National Expert	Software	SCD & THAL 07/05/2024	SCD Expected 31/12/2024	THAL Expected 31/12/2024	SCD&THAL Expected 31/12/2024
Belgium	Belgian Registry of Sickle Cell Disease and Rare Anemia Patients (BR-ScRa)	Béatrice Gulbis Laurence Dedeken	REDCAp - Custom	**573**	606	70	**676**
Cyprus	Archbishop Makarios III Hospital	Soteroula Christou Iren Savvides	REDCap - RADeep	**2**	40	600	**640**
Denmark	Copenhagen University Hospital – Rigshospitalet	Andreas Glenthøj Marianne Hoffmann	RADeep	**75**	60	60	**120**
France	AP-HP Henri-Mondor AP-HP Henri Mondor AP-HP Necker-Enfants Malades AP-HP Robert Debré AP-HP Robert Debré Marseille Hospital	Frédéric Galacteros Pablo Bartolucci Mariane de Montalembert Malika Benkerrou Valentine Brousse Catherine Badens	SCD - Custom SCD - RADeep SCD - RADeep SCD - RADeep THAL - Custom	**0**	475*	640	**1.115**
Germany	Heidelberg University Hospital	Joachim Kunz Andreas Kulozik	Marvin - Custom	**0**	0	150	**150**
Greece	Aghia Sophia Children's Hospital Laiko General Hospital Athens	Antonis Kattamis Maria Dimopoulou	REDCap - RADeep	**114**	250	400	**650**
Ireland	Children's Health Ireland Our Lady's Children Hospital, Crumlin	Emma Tuohy Corrina McMahon	REDCap - RADeep	**0**	-	-	**0**
Italy	Italian Pediatric Hematology Oncology Association (AIEOP)	Raffaella Colombatti Giovanna Russo	RADeep	**737**	750	1002	**1.752**
The Netherlands	University Medical Center Utrecht	Eduard van Beer Karin Fijn van Draat	Castor - Custom	**0**	250	50	**300**
Norway	Lovisenberg Hospital Oslo University Hospital	Marte Holmboe Berg Tina Treu Os	MedInsight - Custom	**0**	80	0	**80**
Portugal	Coimbra University Hospital Centre	Celeste Bento Paula Kjollerstromrs	RADeep	**0**	600	80	**680**
Spain	Spanish Society of Pediatric Hematology and Oncology (SEHOP)	Elena Cela Jose Marco	REDCap - Custom	**808**	762	181	**943**
Sweden	Skane University Hospital	Ulf Tedgard Peter Priftakis	Custom	**0**	300	300	**600**
TOTAL				**2.309**	**4.173**	**3.533**	**7.706**

*Number of patients from AP-HP Robert Debré to be defined

Governance and Steering and Data Access Committee



Annual survey on RADs Disease population

Registry Population

Disease Population

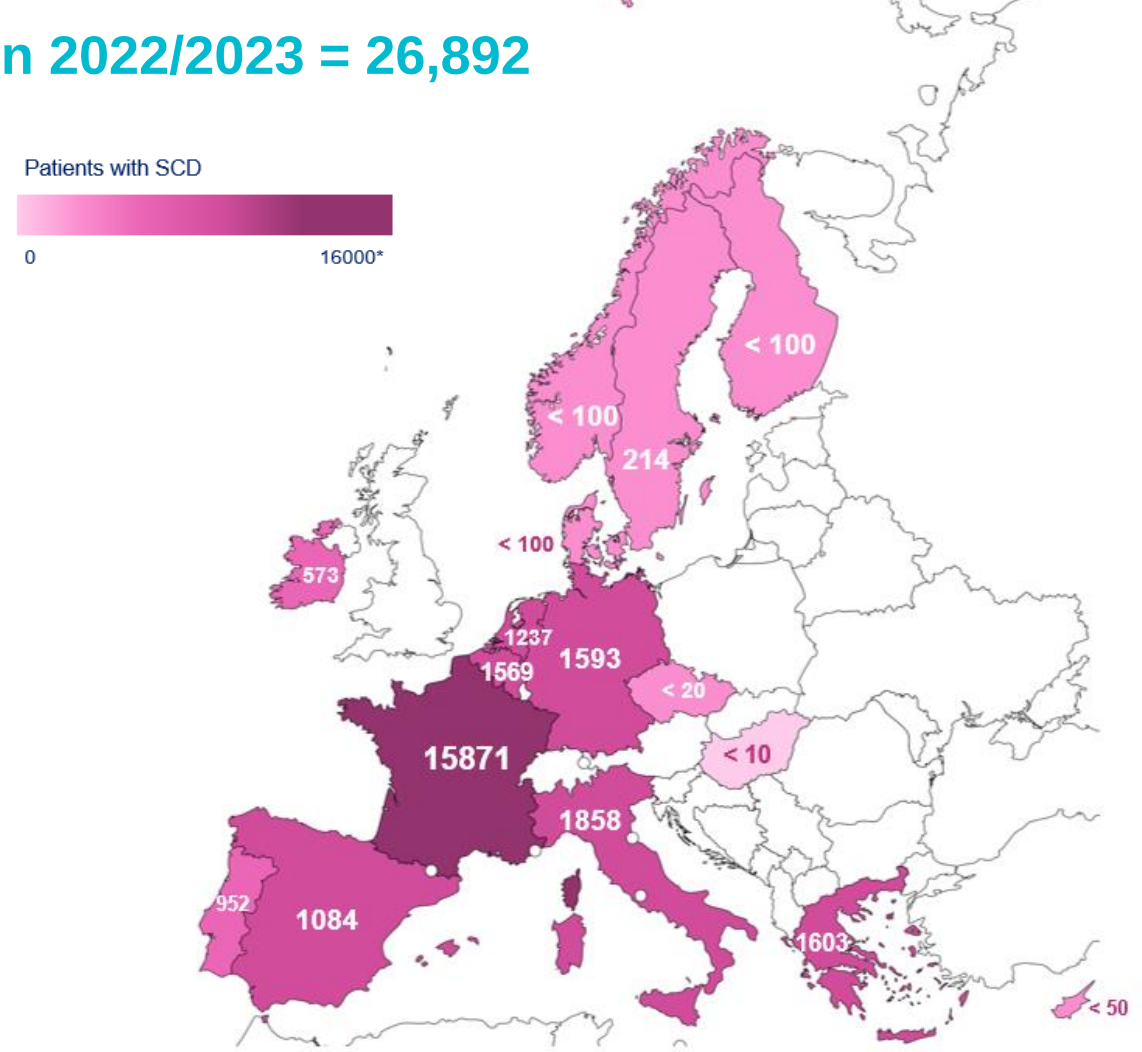
= Representativeness

- Coverage
- Source of bias

Disease Population = 43,914 RADs Patients in 19 EU countries

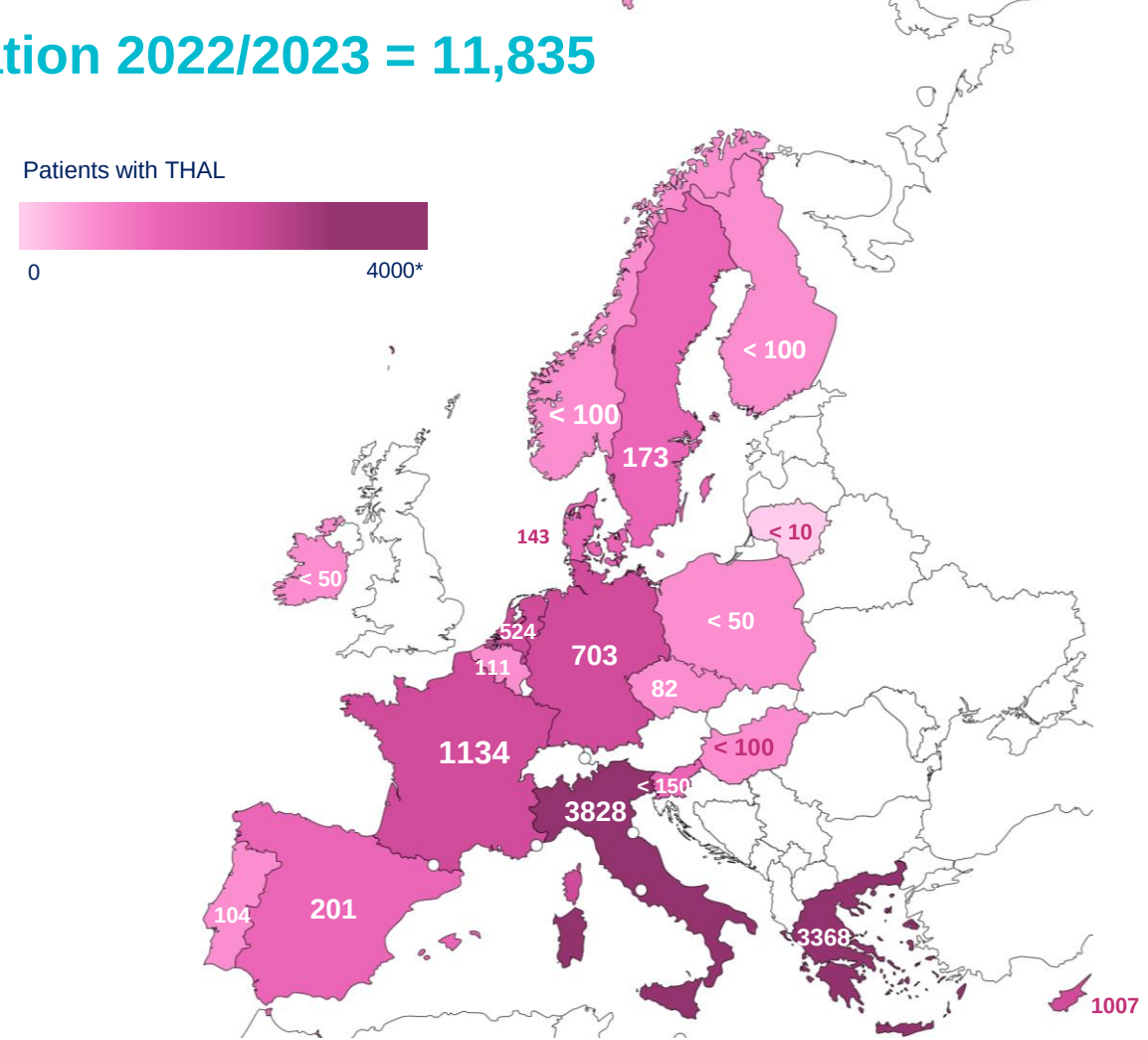
SCD Disease population 2022/2023 = 26,892

Country	SCD		
	Number of centres	Baseline 2022/2023	Pediatric %
Belgium	14	1569	49,0
Cyprus	2	49	24,5
Czech Republic	4	15	53,3
Denmark	2	98	36,7
Finland	1	86	52,3
France	26	15871	40,9
Germany	32	1593	79,1
Greece	24	1603	12,4
Hungary	1	6	0,0
Ireland	1	573	58,5
Italy	32	1858	50,9
Lituania	-	-	-
The Netherlands	6	1237	43,7
Norway	5	84	48,8
Poland	-	-	-
Portugal	8	952	78,1
Slovenia	-	-	-
Spain	54	1084	75,4
Sweden	11	214	72,7
Total	**223**	**26.892**	**46,7**



THAL Disease Population 2022/2023 = 11,835

Country	THAL		
	Number of centres	Baseline 2022/2023	Pediatric %
Belgium	9	111	47,0
Cyprus	3	1007	15,9
Czech Republic	4	82	37,9
Denmark	3	143	24,6
Finland	1	66	47,0
France	25	1134	41,2
Germany	33	703	62,3
Greece	24	3368	15,0
Hungary	1	94	-
Ireland	1	49	34,7
Italy	33	3828	19,2
Lituania	1	2	0,0
The Netherlands	9	524	40,5
Norway	4	97	64,9
Poland	1	49	65,3
Portugal	7	104	25,0
Slovenia	1	100	-
Spain	28	201	52,2
Sweden	9	173	69,4
Total	**197**	**11.835**	**26,1**



Annual survey on RADs disease population – 2022 / 2023

Stratified by severity parameters – Source of bias

	SCD Total			beta-THAL			alfa-THAL		
Country	2 or more VOC %	Transfusion %	HU %	Transfusion pediatric %	Transfusion adult %	Transfusion total %	Transfusion pediatric %	Transfusion adult %	Transfusion total %
Belgium	31,8	10,1	58	62,1	79,3	70,7	0	16,7	11,1
Cyprus	5,1	7,7	56,4	60,6	100	95,4	0	1,7	1,3
Czech Republic	8,3	8,3	25	25	100	57,1	0	0	0
Denmark	4,9	12,2	54,9	53,8	39,1	42,4	22,2	5	10,3
Finland	-	-	-	-	-	-	-	-	-
France	11	7	43,1	75	31,8	33,7	0	0	0
Germany	8,2	3,4	81,5	79,6	89,6	81,1	13,3	0	12,5
Greece	22,8	35,9	108,5	44,2	86,5	83,9	20	16,7	17,2
Hungary	66,7	33,3	66,7	-	0	13,8	-	-	-
Ireland	15,2	28,3	48	81,8	81,8	81,8	-	-	0
Italy	-	-	-	59,8	67,5	66,5	0	9	6,3
Lituania	14,9	18,2	49,3	-	-	-	-	-	-
The Netherlands	4,8	4,4	29	35,8	50,3	46,5	2,4	7,7	5,6
Norway	-	-	-	45,8	72,2	53	75	66,7	72,7
Poland	28,6	14,3	81	0	0	0	0	0	0
Portugal	-	-	-	28,6	23,3	24	-	-	-
Slovenia	24,7	6,5	26,4	-	-	-	-	-	-
Spain	20,4	3,8	69,6	62,5	31,3	50	0	33,3	33,3
Sweden	10,1	15,9	73,9	70,4	100	77,8	14,3	33,3	20
Total	**13,2**	**9,8**	**47,8**	**63,7**	**69,8**	**68,6**	**6,6**	**5,8**	**6,1**

SCD= Sickle cell disease; THAL= Thalassemia; Hb= Hemoglobinopathies; VOC= Vaso-occlusive crisis; HU= Hydroxyurea

RADeep- Data Quality Plan

- Data Quality Plan based on the EMA framework for Patient Registries
- Data quality metrics for RWD

✓ **Relevance**

The design of the Registry protocol and the eCRF involves multiple discussions among experts in RADs from different countries. Annual revision of the eCRF done by the Steering and Data Access Committee

✓ **Coherence**

Data standardization including international codification/ontologies, planification of data collection through an eCRF, web-based application / REDCap to enter the data.

✓ **Timeliness**

Possibility to collect data retrospectively and prospectively
Longitudinal design for data collection

Data Type	Ontologies/Standards
Diagnosis	ORPHA, HGNC, HGVS
Clinical Manifestations	HPO, SNOMED-CT, SCDO
Laboratory Tests	LOINC
Treatments	ATC

RADeep - Data Quality Plan

✓ **Reliability: precision, accuracy and plausibility**

Real-Time: Conditions, Validations, Help texts

Asynchronous: Prevention of duplicates, Validations

Real-time Validation Checks	Validation Method
Sub-diagnosis: Based on the diagnosis that the user will select, a set of the most compatible sub-diagnosis is displayed.	Conditions
Out-of-range values: Lab test results and drug doses are checked whether they are inside an accepted range of values as agreed in eCRF. Otherwise, a warning is popped- up	Validation

✓ **Extensiveness: completeness and coverage**

Real-Time: Mandatory fields

Asynchronous: Reports showing the proportion of registered cases with missing values (or unknown) for all the mandatory variables.

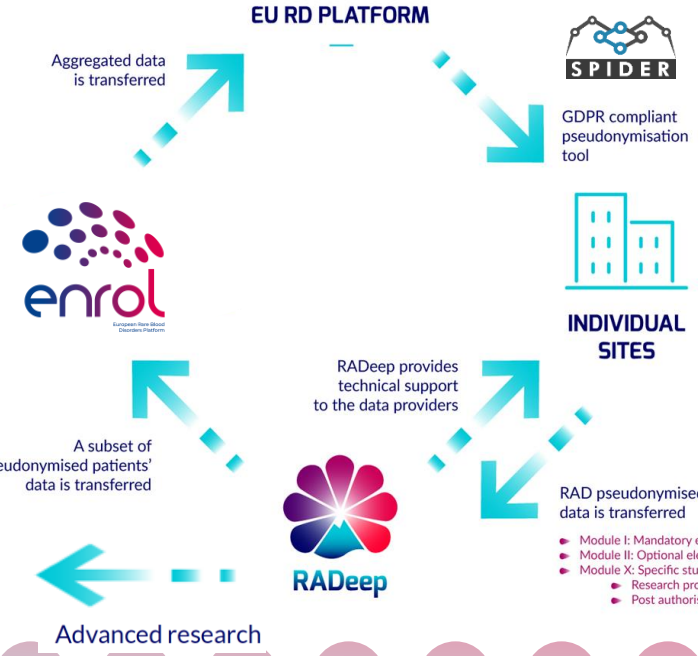
Data driven research

- Linking RWD sources: clinical (EHRs), research (Genomics, Metabolomics, functional studies) and patient self-reported data (PROMs, Health forms, socio-economic) to advance research in SCD, THAL and other RADs.

ERICA
European Rare Disease Research Coordination and Support Action

EUROPEAN JOINT PROGRAMME RARE DISEASES

Data driven AI models for personalized medicine and synthetic data generation in hematology



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ERDERA
EUROPEAN RARE DISEASES RESEARCH ALLIANCE

SYNTHEMA

GEN MED 4ALL

REDCap
Research Electronic Data Capture

ebn
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Data driven research

- Linking RWD resources: clinical (EHRs), research (Genomics, Metabolomics, functional studies) and patient self-reported data (PROMs, Health forms, socio-economic) to advance research in SCD, THAL and other RADs.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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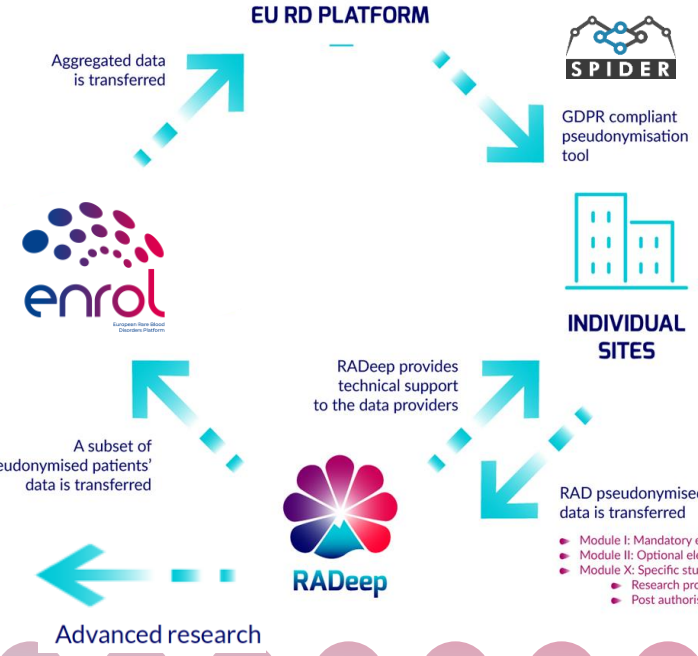
Data driven AI models for personalized medicine and synthetic data generation in hematology



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Next steps / New modules

- Use of the registry (RWD) to support regulatory decision-making on medicinal products within the EU (by generating RWE).

➢ Pre authorisation phase:

- Support registry-based randomised controlled trials (RRCTs) (p.e. patient recruitment)
- External control arm for clinical trials (p.e. endpoints identification, data collection and study follow-up)

➢ Post authorisation phase:

- Developement of a Safety and Efficacy module: To enable EU non-interventional post authorisation safety (PASS), efficacy (PAES) and drug utilisation studies.

RADeep Coordination

Maria del Mar Mañú Pereira
Coordinator

Anna Collado Gimbert
Clinical Research

Sara Reidel
Biostatistician and Data Manager

Maria Rodríguez Sánchez
Data Monitor

Béatrice Gulbis
Co-Coordinator

Ines Labidi
Project manager

Raquel Mosull
Project manager

Claire Diot Lefebvre
Financial and Legal Manager

Petros Kountouris
Co-Coordinator

Stella Tamana
Platform developer

Kalia Orphanou
Platform developer

RADeep Steering and Data Access Committee

Country	Member	Institution	Role
Spain	María del Mar Mañú Pereira	University Hospital Vall d'Hebron - Vall d'Hebron Research Institute, Barcelona.	Steering Committee member – Coordinator
Belgium	Béatrice Gulbis	Hôpital Erasme - Cliniques Universitaires de Bruxelles, Brussels.	Steering Committee member - Co – Coordinator
Cyprus	Petros Kountouris	Cyprus Institute of Neurology and Genetics, Nicosia.	Steering Committee member - Co – Coordinator
Spain	Anna Collado Gimbert	University Hospital Vall d'Hebron - Vall d'Hebron Research Institute, Barcelona.	Steering Committee member - Clinical Researcher
Spain	Sara Reidel	University Hospital Vall d'Hebron - Vall d'Hebron Research Institute, Barcelona.	Steering Committee member - Biostatistician
Cyprus	Stella Tamana	Cyprus Institute of Neurology and Genetics, Nicosia.	Steering Committee member - Platform manager
Italy	Raffaella Colombatti	Azienda Ospedaliera di Padova, Padova.	Steering Committee member - Paediatrician
The Netherlands	Eduard van Beers	University Medical Center Utrecht, Utrecht.	Steering Committee member - Haematologist
Italy	Paola Bianchi	Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan.	Steering Committee member - Laboratory specialist
Italy	Loris Brunetta	Associazione Ligure Thalassemici Onlus.	Steering Committee member - Patients' representative
The Netherlands	Dore Peereboom	Stichting Zeldzame Bloedziekten.	Steering Committee member - Patients' representative
Belgium	Laurence Dedeken	Hôpital Universitaire des Enfants Reine Fabiola (HUDERF), Brussels.	Data Provider
Cyprus	Soteroula Christou	Archbishop Makarios III Hospital, Nicosia.	Data Provider - National Registry
Cyprus	Iren Savvides	Archbishop Makarios III Hospital, Nicosia.	Data Provider - National Registry (substitute)
Denmark	Andreas Glenthøj	Rigshospitalet, Copenhagen.	Data Provider
Denmark	Marianne Hoffmann	Rigshospitalet, Copenhagen.	Data Provider (substitute)
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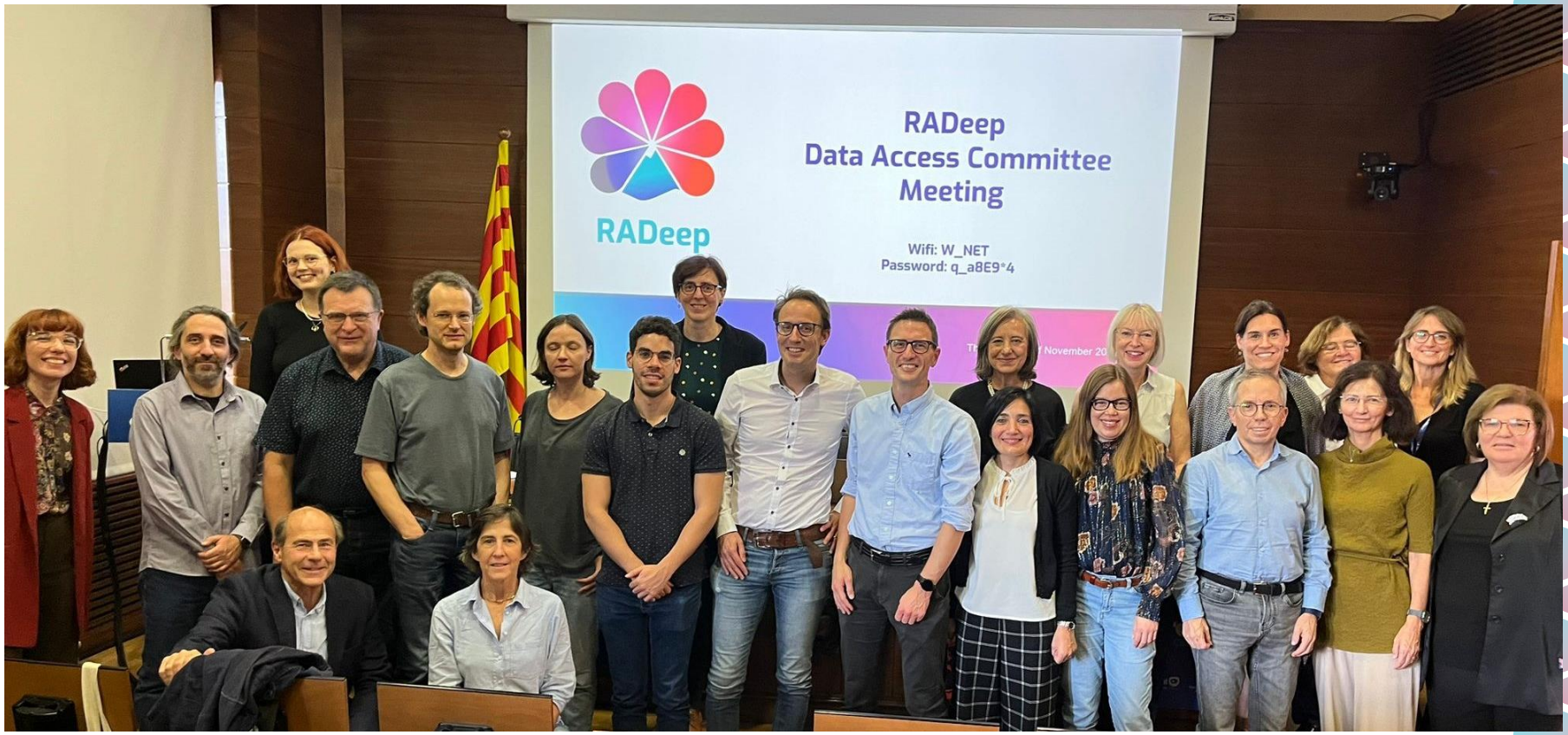
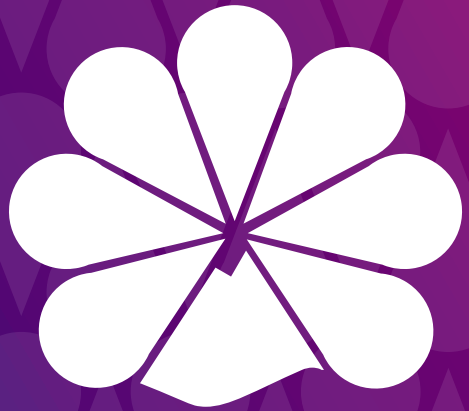
France	Pablo Bartolucci	Assistance Publique - Hôpitaux de Paris - Hôpital Henri Mondor, Paris.	Data Provider (substitute)
Germany	Joachim Kunz	Heidelberg University, Heidelberg.	Data Provider - German Rare Anaemia Registry
Germany	Andreas Kulozik	Heidelberg University, Heidelberg.	Data Provider - German Rare Anaemia Registry (substitute)
Greece	Antonis Kattamis	University of Athens - Aghia Sophia Children's Hospital, Athens.	Data Provider
Greece	Ilona Binenbaum	University of Athens - Aghia Sophia Children's Hospital, Athens.	Data Povider (substitute)
Italy	Giovanna Russo	Azienda Ospedaliero Universitaria Policlinico "Rodolico-San Marco", Catania.	Data Provider - AIEOP registry
Italy	Daniela Cuzzubbo	Ospedale Pediatrico Meyer Firenze.	Data Provider - AIEOP registry (substitute)
Portugal	Celeste Bento	Centro Hospitalar e Universitário de Coimbra, Coimbra.	Data Provider - National Registry
Portugal	Paula Kjollerstrom	Hospital Dona Estefania.	Data Provider - National Registry (substitute)
Spain	Elena Cela	Hospital Gregorio Marañón, Madrid.	Data Provider - SEHOP Registry
Spain	Jose Marco	Hospital Gregorio Marañón, Madrid.	Data Provider - SEHOP Registry (substitute)
Spain	Maria Pilar Nicolas	Facultad de Derecho/Zuzenbideko Fakultatea/Faculty of Law.	Legal expert
Spain	Iñigo de Miguel Beriain	Facultad de Derecho/Zuzenbideko Fakultatea/Faculty of Law.	Legal expert
Spain	Alexis Rodriguez Gallego	Vall d'Hebron Research Institute, Barcelona.	Ethical expert
Sweden	Ulf Tedgard	Skåne University Hospital, Lund.	Data Provider - VPH Registry
Sweden	Annika Martensson	Skåne University Hospital, Lund.	Data Provider - VPH Registry (substitute)
The Netherlands	Karin Fijn van Draat	Amsterdam UMC.	Data Provider - SCORE

RADeep Steering and Data Access Committee





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