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European Reference Network for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

European Reference Networks

DELIVERABLE 8.2 ERN-EUROBLOODNET REPORT ON ACTIONS TO FOSTER EPIDEMIOLOGICAL SURVEILLANCE ON RHD 2

ERN-EuroBloodNet
European Reference Network on Rare Hematological Diseases

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DOCUMENT INFORMATION

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Report

ERN: **ERN-EuroBloodNet (European Reference Network on Rare Hematological Diseases)**

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Authors:

Maria del Mar Mañú Pereira – ERN-EuroBloodNet Scientific Director

Victoria Gutierrez Valle – ERN-EuroBloodNet Dissemination & IT Manager

Béatrice Gulbis - ERN-EuroBloodNet co-Coordinator and non-Oncological Hub chair

Pierre Fenaux - ERN-EuroBloodNet Coordinator and Oncological Hub chair

Short Description

Report on activities implemented by ERN-EuroBloodNet to foster epidemiological surveillance of RHD. It includes the introduction of ENROL as the European Rare Blood Disorders Platform for patients registration.

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1. INTRODUCTION

EUROPEAN CONTEXT OF RARE HEMATOLOGICAL DISEASES EPIDEMIOLOGICAL SURVEILLANCE

ERN-EuroBloodNet disease coverage results in more than 450 different entities with differential clinical and etiological features i.e. oncological vs non-oncological, hereditary vs acquired, or significant difference frequency, among others. Most of Rare Hematological Diseases (RHDs) can cause chronic health problems and many of them are life-threatening requiring numerous resources and multidisciplinary teams for their correct diagnosis, management and treatment, representing a public health challenge.

However, as for other rare diseases (RDs), it is often challenging to bring together sufficient patients data, due to their low prevalence compounded by the fact that problems often arise in achieving an accurate diagnosis, especially for less prevalent diseases. Moreover, standards governing collection, organization, or availability of RD patients data have been lacking until recently, leading to large number of unstructured and non-interoperable sources of information at national, regional, and local levels that have been running for last decades.

Fragmentation and lack of interoperability between the data sources still is a key obstacle for epidemiological, clinical, translational and pharmacological studies and research, as no single institution or even no single country has enough patients in order to sustain basic, clinical, epidemiological research or pharmacological trials.

By making existing registries on RHDs interoperable at a European level, researchers from several countries will be able to share the data with their counterparts across the world.

EUROPEAN COMMISSION STRATEGY FOR RARE DISEASE PATIENTS POPULATION MONITORING & REGISTRATION

European Reference Networks Monitoring System: Patients population

Member States (MS), ERNs and European Commission (EC) have established a solid continuous monitoring system of the ERNs to allow a closer follow up of the activities performed by the networks based on a set of 18 Core indicators gathered among ERN members every six months. One of the key pillars of the monitoring system is related to the assessment of ERNs total population relying on the aggregated number of patients looked after by each of the HCPs of a given ERN.

The aggregated total number of patients of an ERN will be the backbone of the ERNs capabilities as the pooling of the data and information provided by this population of patients will feed the whole system of ERNs and make possible the generation of knowledge and new evidence for the better diagnosis and treatment of those patients. A first estimation of the ERN-EuroBloodNet members activity based on number of patients can be found at Deliverable 8.1 ERN-EuroBloodNet report on actions to foster epidemiological surveillance on RHD, June 2020.

European Reference Networks Rare Disease patient registries

Patient registries and databases constitute key instruments to develop clinical research in the field of RD, to improve patient care and healthcare planning. They are the best way of pooling data to achieve a sufficient sample size for epidemiological and/or clinical research. Registries serve as a recruitment tool for the launch of studies focusing on disease etiology, pathogenesis, diagnosis or therapy.

The Council of the European Union recommended that, in the field of rare diseases, MS consider supporting at all appropriate levels, including the EU level, for epidemiological purposes, registries and databases, whilst being aware of independent governance. In order to support this process and, in particular, the interoperability of data in rare diseases registries, the Commission decided to set up a European Platform on Rare Disease Registration (EU RD Platform) and to develop specific standards for the interoperability of such rare disease registries ("JRC standards" developed by the Commission's Joint Research Centre).

As foreseen in Article 12 of the Directive on the application of patients' rights in cross-border healthcare, 24 ERNs were kicked-off in 2017 and since 2018 they are developing their research capabilities. Patient registries belong to this development, enabling to build patients cohorts at European level to follow up the natural course of diseases with sufficient patients data.

In this context, the 21st May 2019, Chafea opened the call HP-PJ-2019 for supporting the development of RDs registries for the ERNs aiming to enable building, upgrading, linking and making interoperable registries covering the diseases of each ERN. By following the standards defined by the EU RD Platform, ERN registries will be able to link and make visible patients cohorts at European level in order to follow up the natural course of diseases with sufficient patients data. Importantly, patient registries will also contribute to the ERNs evaluation process foreseen in the ERN implementing decision and to the continuous monitoring and quality improvement system of the networks.

ERN-EuroBloodNet proposal for the implementation of the European Rare Blood Disorders Platform (ENROL) was approved for funding (GA 947670) and officially started 1st June 2020.

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EUROPEAN RARE BLOOD DISORDERS PLATFORM (ENROL)

The European Rare Blood Disorders Platform (ENROL) is conceived as the ERN-EuroBloodNet umbrella platform for both new and already existing registries on Rare Hematological Diseases (RHDs) avoiding fragmentation of data by promoting the interoperability standards for patient registries in line with the EU RD Platform. ENROL is officially endorsed by the European Hematology Association (EHA).

ENROL's Principle is to maximize public benefit from data on RHDs opened-up through the platform with the only restriction needed to guarantee patient rights and confidentiality, in agreement with EU regulations for cross-border sharing of personal data. Accordingly, ENROL aims at EU-wide mapping of demographics, survival rates, diagnosis methods, genetic information, main clinical manifestations and treatments in order to obtain epidemiological figures and identify trial cohorts for basic and clinical research. To this aim, ENROL will connect and facilitate upgrading of existing RHD registries, while promoting the building of new ones when / where lacking.

A first exploratory exercise on existing registries for RHD was performed in the third year of ERN-EuroBloodNet, allowed the creation of a first list of EU-RHD Registries allowing the identification of a total 184 registries including a first overview of the list of registries identified by ORPHANET covering RHD (Report May 2019) and other EU-RHD registries identified reported by members and by literature review. The methodological approach and detailed results are available at Deliverable 8.1 ERN-EuroBloodNet report on actions to foster epidemiological surveillance on RHD, June 2020.

2. OBJECTIVES

In line with the ERN-EuroBloodNet "Specific Objective 5. Foster European cooperation in highly specialized procedures for diagnosis, innovative treatments and research", the present deliverable aims to detail the activities implemented to foster epidemiological surveillance of RHD in the frame of the European Commission strategy for RD patients population monitoring and registration, and in concrete:

- To estimate the patients population within ERN-EuroBloodNet members
- To update the mapping exercise for the creation of an inventory of EU-RHD registries
- To support the development of ENROL pilots for domain specific RHD
- To establish synergies with other ERNs for the implementation of rare disease patients registries

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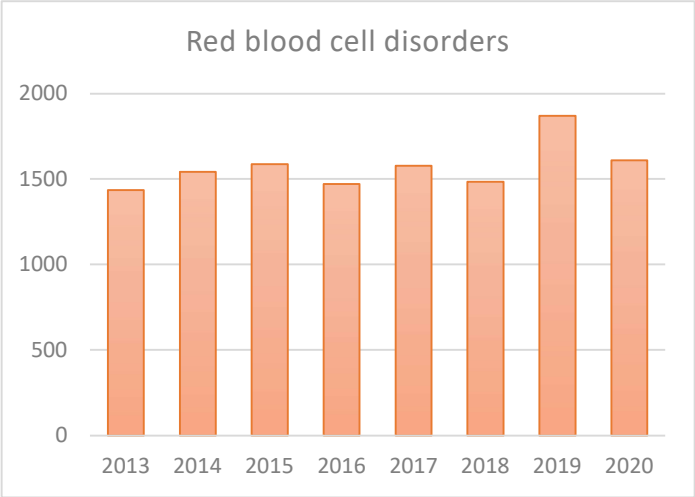
3. ACTIONS

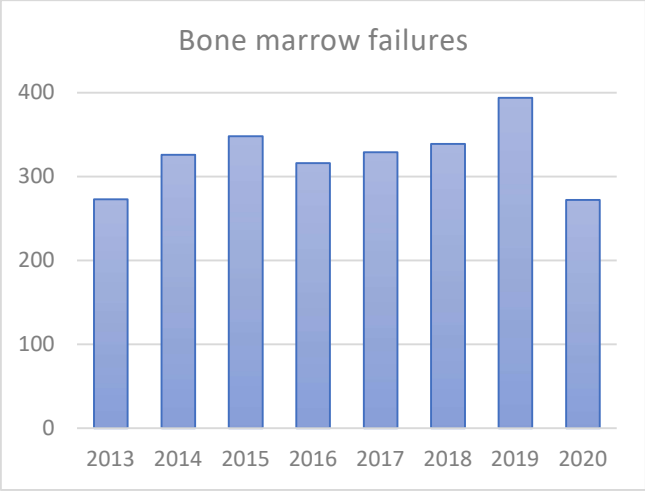
ESTIMATION OF THE ERN-EUROBLOODNET MEMBERS ACTIVITY BY NUMBER OF PATIENTS

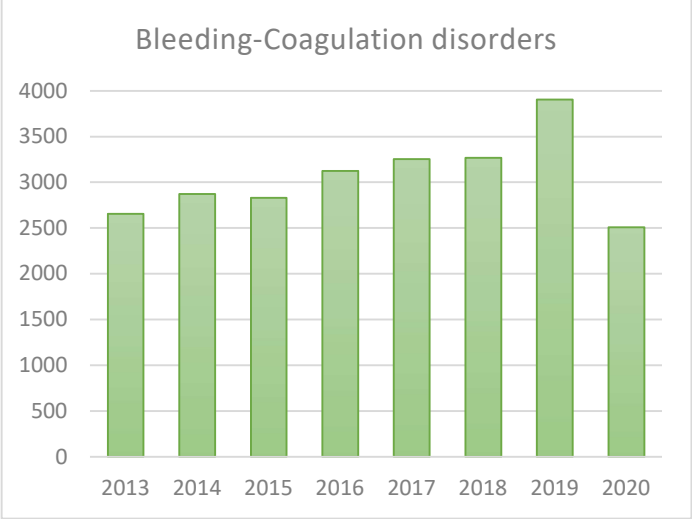
ANALYSIS OF NUMBER OF PATIENTS REPORTED BY ERN-EUROBLOODNET MEMBERS PER SUBNETWORKS

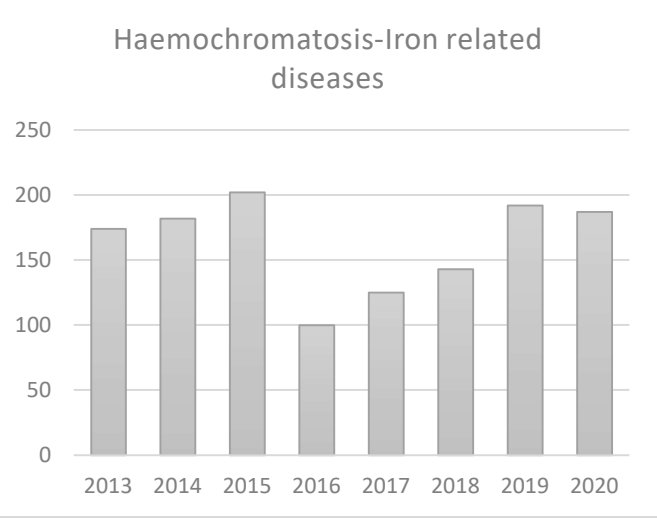
ERN-EuroBloodNet monitoring exercises are performed by the coordination team based on the conduction of an excel template including number of patients by disease/disease group reported at the time of ERN application, and dedicated cells to be completed each monitoring period, including a) number of patients/year by diseases, b) number of new patients/year by diseases. Templates are circulated among members representatives and multidisciplinary teams. Moreover, Affiliated partners have been included in the process since last monitoring exercise.

The number of patients by disease/disease group compiled through the monitoring exercises conducted so far has been grouped by subnetwork in order to provide a better idea of patients population by major disease areas covered by the network. The following Figs 1-6 represent the number of new patients reported by the ERN-EuroBloodNet members in the membership application form and consecutive monitoring exercises in the different subnetworks:









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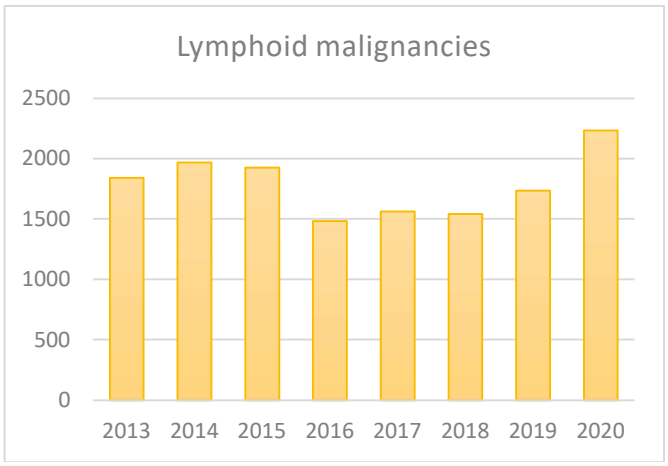
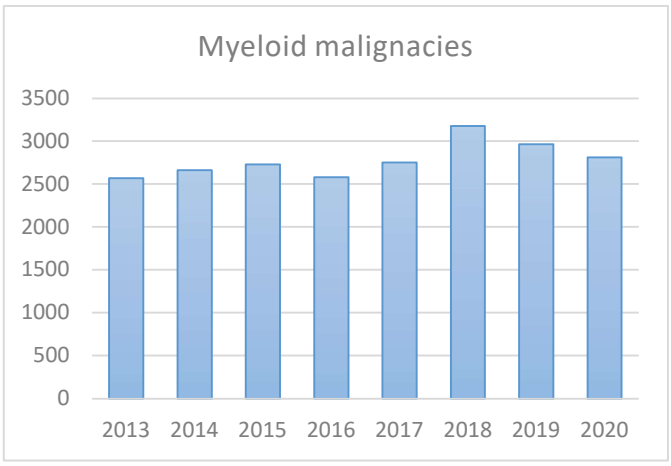
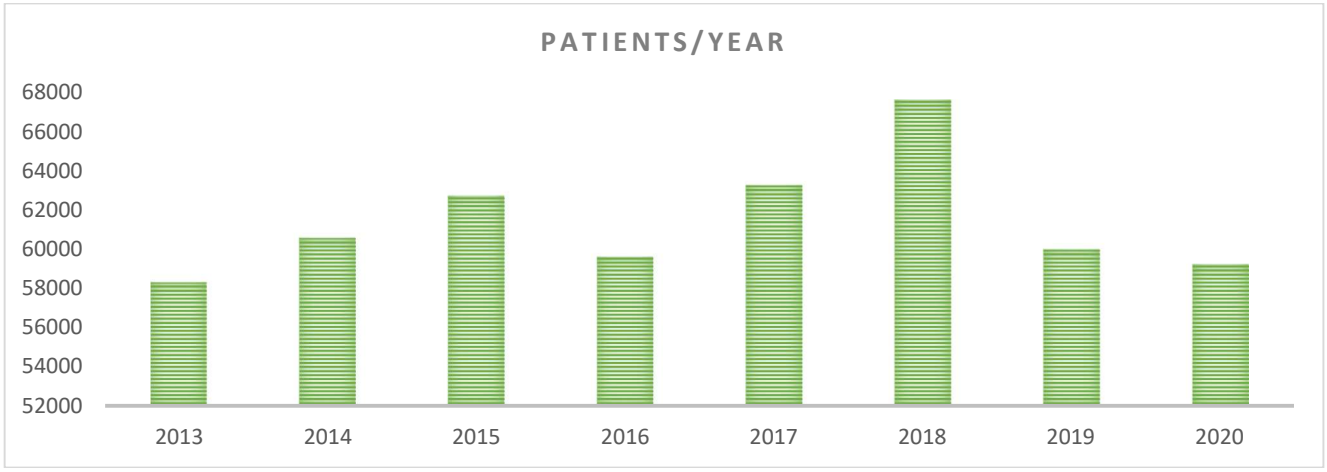




Figures 1-6. Number of new patients per year by subnetwork.

The total number of patients / year and the number of new patients/ year can be found in the Figs. 7-8.



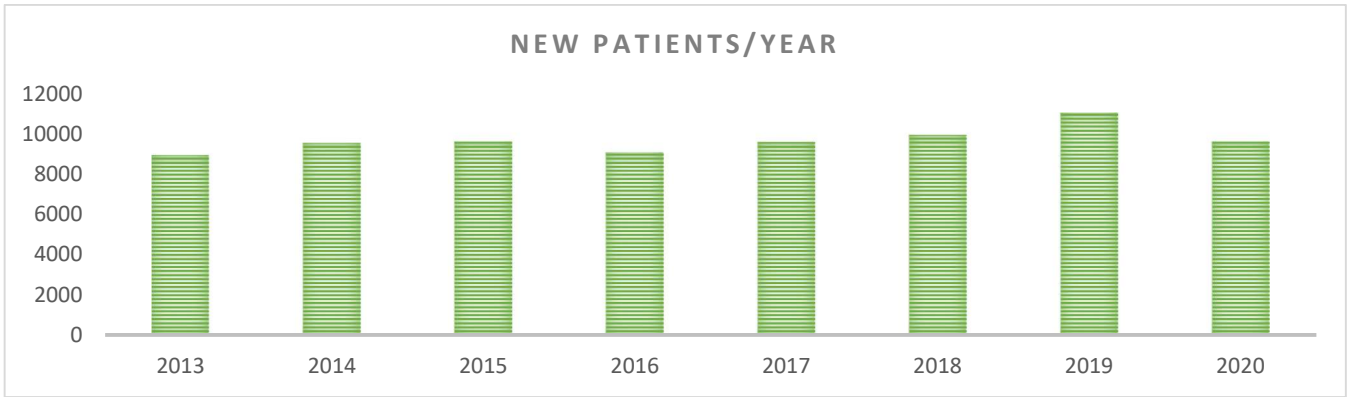


Fig. 7 and 8. Number of patients and New patients per year gathered from ERN-EuroBloodNet membership proposals and monitoring exercises.

It is necessary to highlight that these numbers present different bias that have to be taken into consideration for the analysis, mainly due to two major reasons: a) Differences of the % of HCPs members participating in the monitoring exercises, b) Partial data provided by the members participating in the monitoring. For example, some HCPs reported data on big group of diseases, while other HCPs reported data on very concrete disorders. Whilst both approaches are correct for the reporting monitoring exercises, a harmonization towards the analysis by subnetworks and disease groups is required in order to better understand the picture of the current situation of RHD number of patients within the network.

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In this context, for example the slight decrease of the numbers reported in 2016 is due to the participation of 56 HCPs in the monitoring exercise, representing 84,8% of the ERN-EuroBloodNet members. Moreover, the decrease of the data available for analysis is exacerbated by the fact that not all of them provided full data on their disease-areas coverage, but partial data (ie. only for some subnetworks covered under their expertise).

Although the trends of the number of new patients have been maintained in years, a slight decrease has been observed in 2020, which could be explained for two main reasons: the impact of COVID pandemic on the health professionals time that can dedicate to ERNs activities as for the participation in the monitoring exercise, and the impact of Brexit (6 members were opted out from ERN-EuroBloodNet). Moreover, although Affiliated Partners were requested to participate in the last exercise, the engagement of the new partners still needs to be consolidated for a better contribution in the network activity, including the monitoring actions.

Another aspect that can be identified in these exercises is the difference among the number of new/patients and the decrease of total number of patients. This could be explained due to a higher contribution of the members to the indicator, which specifically refers to "new patients", while the total number of patients could be more difficult to be tracked at the hospital Electronic Health Records and that may be impacting in the last exercises where COVID constraints were already present.

The implementation of a dedicated tool at ERN-EuroBloodNet website for self reporting number of patients on RHD disease groups is expected to increase the number and comparability of data.

All in all, these challenges for the performing of a reliable data analysis evidence the urgent action required for a European approach that would allow the gathering of patients data in a structured and harmonized way. This first approach sheds light on the approximate number of patients by subnetwork followed by ERN-EuroBloodNet and therefore, potentially registered through ENROL platform for the adequate exploitation and data analysis on RHD.

UPDATE OF THE INVENTORY OF EU-RHD-REGISTRIES

Based on the exploratory exercise performed in the third year of ERN-EuroBloodNet implementation, the list of National/European and international registries on RHDs has been updated/expanded with literature review and online search and feedback from ePAGs, allowing the identification of 242 registries with a European Member State (EU-MS) coverage, including also non-European countries coordinating initiatives with a global and international coverage. This result represents an expansion in 59 registries in comparison with the previous exercise (June 2020). Final list was classified on RHD disease groups and country coverage, and including when available coordinating country, geographical coverage, curator etc.

The mapping exercise includes 4 registries identified with a treatment related scope (ie. bone marrow transplant and transplantation in children) and 9 mutations databases. The 229 patients' registries found present the disease coverage and geographical scope described in Figs 9 and 10.

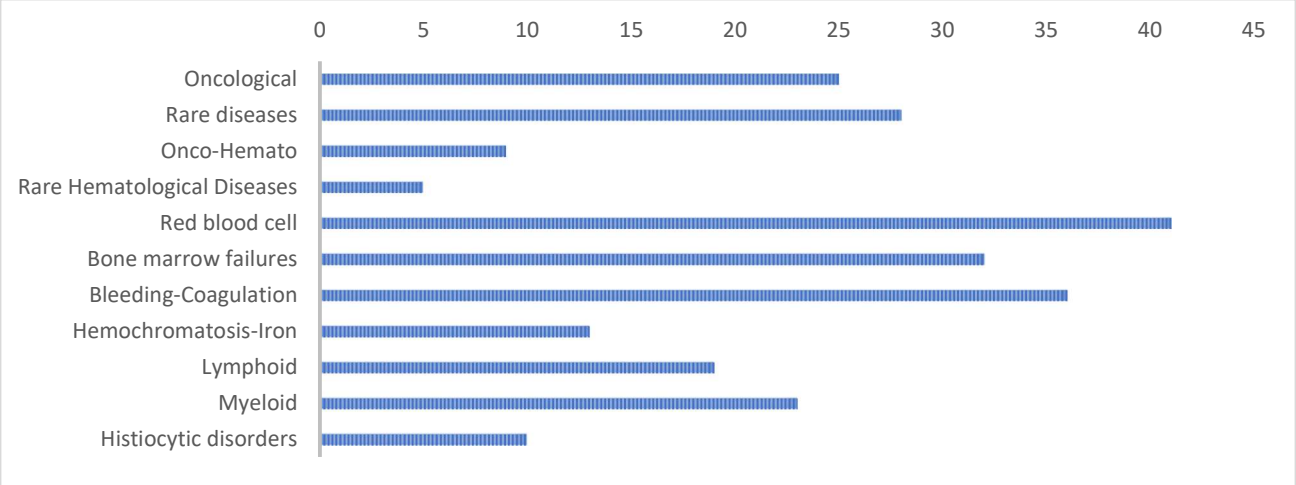

Fig. 9 Number of patients' registries identified and areas covered.

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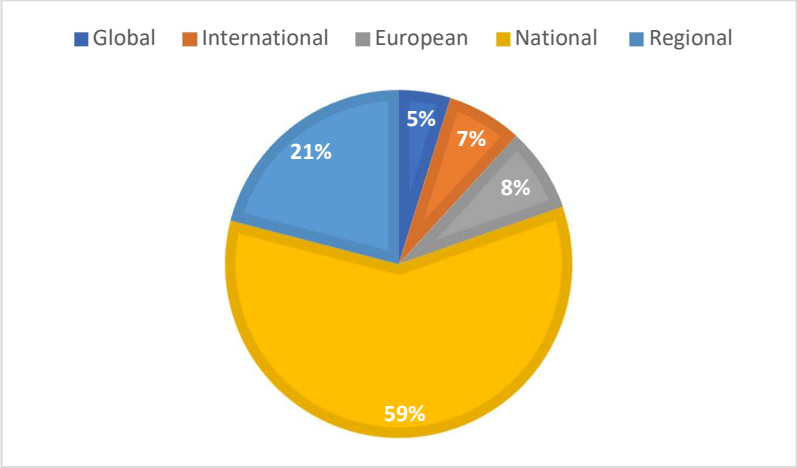

Fig 10. Geographical scope of the patients' registries identified

In the frame of ENROL it is important to stress the identification of the 11 Global, 16 International, 18 European and 136 national initiatives found as key potential contacts to establish collaborations and become ENROL data providers. The detailed coverage by disease areas and subnetworks can be found in Fig. 11. For further details visit ENROL website.

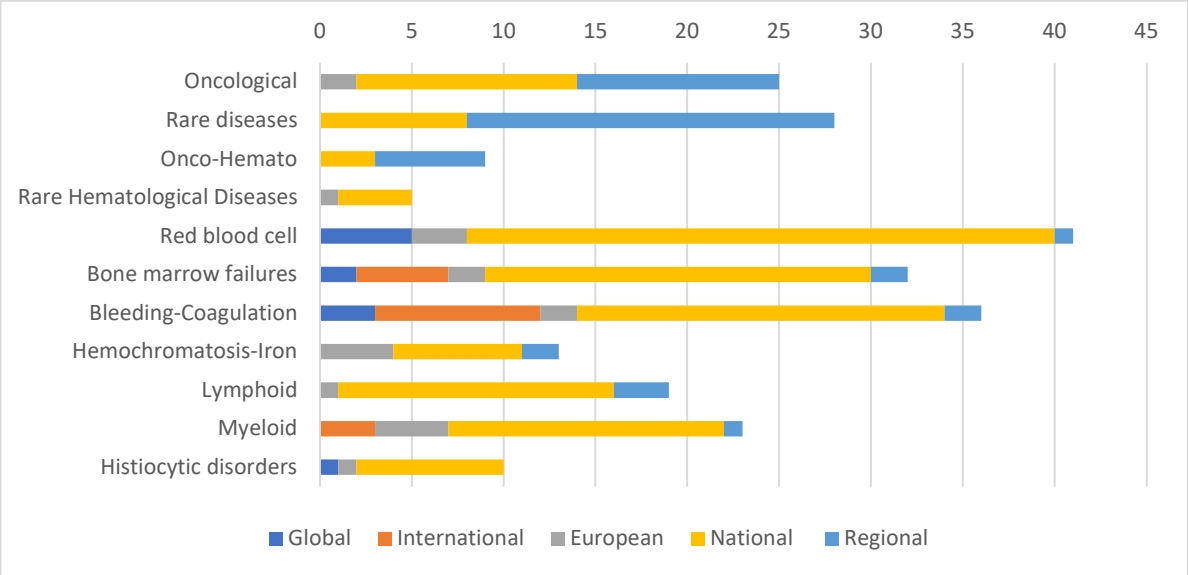

Fig 11. Number of European and Global initiatives per area

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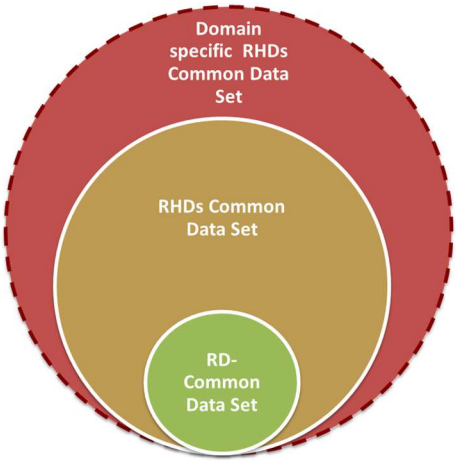
ENROL PILOTS FOR DOMAIN SPECIFIC RHD-CDS: BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM AND RARE ANAEMIA DISORDERS

ENROL is being developed having reviewed all the relevant recommendations particularly concerning interoperability, in order to receive data from existing registries and assist networking. Taking into consideration the wide difference on RHDs entities clinical and etiological nature, ENROL dataset has been conceived in a bottom-up design for ensuring the capture of the common elements for rare diseases in line with the EU recommendations and with the EU RD platform, and the key features common for the whole spectrum for RHDs. Furthermore, the latest level can be stepped up for the definition of domain specific elements that support the in-depth analysis.

Accordingly ENROL common data set (CDS) contemplates the following three-levels-of-depth (Fig. 12)



1. Rare Diseases Common Data Set (RD-CDS) - set of mandatory parameters common to all RDs, essential for ensuring interoperability among European structures for RDs.

2. Rare Haematological Diseases Common Data Set (RHD-CDS) - set of mandatory parameters common to all RHDs, aiming to answer ENROL objectives

3. Domain specific RHD-CDS - set of mandatory/optional parameters common to concrete domains, ie. Rare anaemia disorders, Blastic plasmacytoid dendritic cell neoplasm; or concretely developed for in depth analysis, ie. research oriented studies.

Fig 12. ENROL levels-of-depth CDS

Considering ENROL aims to connect and facilitate upgrading of existing RHD registries, while promoting the building of new ones when / where lacking, RHDs patients' data will be collected through ENROL platform from any EU-MS country combining different sources of data, including a) existing registries and b) Healthcare providers (HCPs) hospital records.

Based on the Inventory of existing EU-RHD registries, two RHD disease groups were targeted as first pilots for the development of Domain specific RHD-CDS in line with ENROL dataset, representing two different scenarios of availability of existing data, therefore requiring the tailor of strategies that could be replicated to other disease groups (further details can be found at ENROL website Disease registries section):

BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM (BPDCN)

BPDCN is a very rare lymphoid disease that requires from highly specialized expertise for the proper diagnosis, being very often misdiagnosed and under reported. BPDCN clinical management requires from multidisciplinary team including hematologists and dermatologists as the skin is the most frequently involved site of the diseases. The prognosis of the disease is approximately 1 year if patient is not transplanted, and there is an urgent need for the development of curative treatments.

The availability of BPDCN patients data at the EU national level greatly varies from one country to another, where the only national database gathering patients data has been identified in France.

Considering the lack of existing registries, after a first contact with the curator of the French database, a collaboration has been established to support the creation of a new European registry on BPDCN with three countries acting as pilots: France, Italy and Germany. National coordinators for the three countries have been already identified and the BPDCN specific CDS is under development in line with ENROL dataset and standards for interoperability implemented. A collaboration agreement will be in place for the transfer of a subset of pseudonymysed patients' data to ENROL.

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RARE ANAEMIA DISORDERS (RADS)

RADs is a group of rare diseases characterized for presenting anaemia as the main clinical manifestation. 132 different medical entities classified as RADs by ORPHA classification being most of them chronic life threating disorders with many unmet needs for their proper clinical management creating an impact on European health systems. RADs present diagnostic challenges and their appropriate management requires from specialised multidisciplinary teams in Centers of expertise.

Although there are some examples of well-established national registries on RADs in EU, the lack of recommendations for Rare disease registries implementation and the lack of standards for interoperability has led to the fragmentation or unavailability of data on prevalence, survival, main clinical manifestations or treatments in most of the European countries.

With this fragmented panorama, the Rare Anaemia Disorders European Epidemiological Platform (RADeep) was launched as an initiative endorsed by ERN-EuroBloodNet for pooling data from patients affected by a RAD built in line with the EU Rare Disease Platform (EU RD Platform). RADeep is open to any national registry and medical center willing to actively collaborate as data providers in EU, starting with a pilot in 9 European countries: Belgium, Cyprus, Denmark, France, Germany, Italy, Netherlands, Portugal and Spain.

In this context, a collaboration has been established with RADeep for facilitating the connection and linkage of existing national registries and databases by supporting their upgrade through the integration of the standards for interoperability promoted by ENROL. RAD specific CDS is under development and a collaboration agreement will be in place for the transfer of a subset of pseudonymysed patients' data to ENROL.

ESTABLISHMENT OF SYNERGIES WITH THE ERNS FOR REGISTRIES IMPLEMENTATION AND EPIDEMIOLOGICAL SURVEILLANCE

The European Rare dIsease research Coordination and support Action (ERICA) project has been established as the structural framework to support of the research activities of the 24 ERNs. ERICA promotes inter-ERN research activities and establish firm collaborative ties with existing European and international infrastructures and consortia involved in rare disease research and innovation while supporting concrete actions on the harmonization of ERNs registries procedures, as the development of Informed consent and data sharing agreement templates.

Moreover, ERICA, together with the European Joint Programme on Rare Diseases (EJP RD) and the Joint Research Center (JRC) are promoting synergies among ERNs for the definition of Domain specific Common Data Elements (DCDEs) with the objective to be able to share domain specific data between ERNs, data that is not currently covered by the Common Data Elements (CDEs). At the stage of the present deliverable, the first of a short series of online meetings have been held including representatives from all the ERNs to finalize the DCDEs.

Finally, a project proposal for Artificial Intelligence and data structuring on RD has been submitted under the call topic HORIZON-HLTH-2021-TOOL-06-03 last September 2021 as a result from a joining effort from 5 ERNs (ERN-EuroBloodNet, MetabERN, ERKnet, ERN-BOND and EndoERN), aiming to develop novel Artificial Intelligence solutions to solve the current challenges of unstructured Electronic Health Records and RD registries, and their lack of interoperability. Such tools would be tested in use-cases of selected rare metabolic, kidney, endocrine, blood and skeletal diseases in accordance with current legislation, ethics, personal data protection, and cybersecurity.

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4. EXPECTED OUTCOMES & NEXT STEPS

The analysis of the RHD population in ERN-EuroBloodNet members and affiliated partners by subnetwork has allowed the structuring and harmonization of data collected through monitoring exercises conducted so far while provided a starting point for ENROL implementation in terms of an estimation on prevalence of patients in follow up for each subnetwork. The main barriers already identified for the analysis of monitoring exercises, have potentiate the urgent need to better address the epidemiological surveillance of these diseases through a well-structured European structure as ENROL that will lead to the harmonized collection of patients data based on common and specific data elements.

RHDs patients' data will be collected through ENROL platform from any EU-MS country combining different sources of data, including a) existing registries and b) Healthcare providers (HCPs) hospital records. The exploratory exercise of existing registries on RHD has allowed the creation of a first list of EU-RHD Registries including a) the list of registries identified by ORPHANET covering RHD (Report May 2019), b) EU-RHD registries identified by previous ERN-EuroBloodNet initiatives, c) Other EU-RHD registries identified by literature review and online search, and d) National / Regional registries for RDs, e) Input from ePAGs, shedding light on the state of the art on available registries on RHDs.

Moreover, their classification into the RHD disease groups, country coverage and scope has allowed the identification of the gaps and needs for the two first pilots for development RHD-CDS definition, tailoring the strategies to be implemented in the different scenarios found, ie. creation of a new European registry, or support the upgrade of existing databases to facilitate the linkage of existing sources.

Also as important remark in the context of interoperability and FAIRification among data sources, collaborations have already been established among all ERNs through the synergies promoted by ERICA, EJP RD and JRC for the establishment of a set of DCDEs in the frame of ERNs patients registries.

By making existing registries on RD interoperable at a European level, researchers from several countries will be able to share the data with their counterparts across the world. Apart from increasing data input, the move will also encourage flow of ideas and collaboration among professionals involved in research and clinical care of patients affected by RD. Making the existing registries interoperable is a major challenge that will directly lead to the exploitation of available data for research and epidemiological surveillance.

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https://ec.europa.eu/health/ern_en

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