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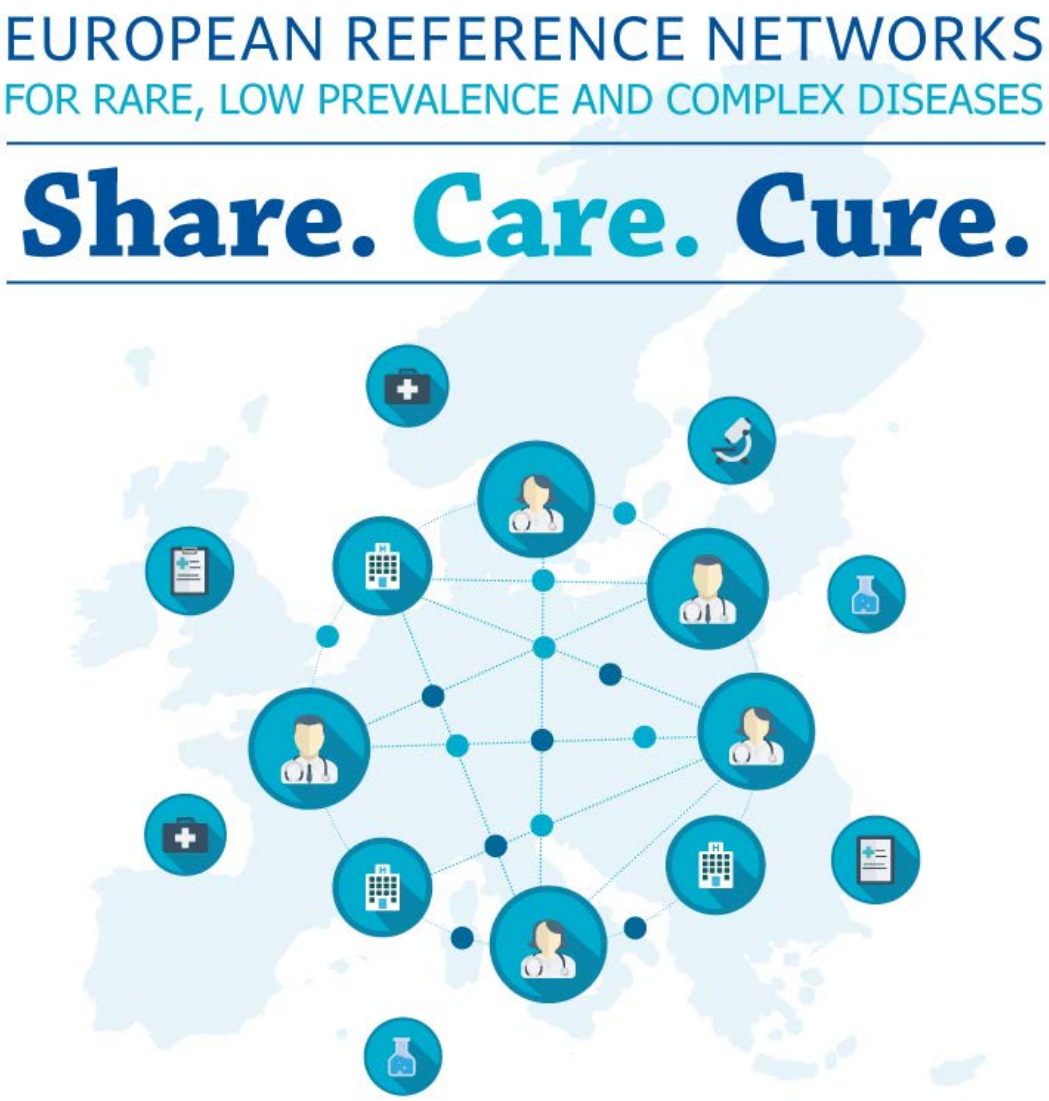
European Reference Network for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

European Reference Networks

8.1 ERN-EuroBloodNet report on actions to foster epidemiological surveillance on RHD

ERN-EuroBloodNet
European Reference Network on Rare Hematological Diseases



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DOCUMENT INFORMATION

ERN-EUROBLOODNET REPORT ON ACTIONS TO FOSTER EPIDEMIOLOGICAL SURVEILLANCE ON RHD

Report

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

Call: **HP-ERN-SGA-2018**

Type of action: **HP-SGA-PJ**

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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

With the possible exception of classical myeloma and chronic lymphocytic leukemia, haematological diseases are rare (ORPHA97992), including myeloid and lymphoid tumors (ORPHA 68347), rare anemia disorders (ORPHA 108997), rare coagulation disorders (ORPHA 98429), and polycythemia (ORPHA 98427). Rare hereditary hemochromatosis (ORPHA220489) was also included in the disease scope of ERN-EuroBloodNet following a request from well-established patient groups and experts. Thus, 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-interoperaberable 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.

This fragmentation of data has a direct impact on RHDs target groups and stakeholders. Patients who often feel isolated and in many occasions have no options for curative treatments, researchers and clinicians who are unable to reach critical numbers for engaging basic and clinical research supporting development of new treatment options, and health authorities who lack for epidemiological and disease burden data for the allocation of resources for best health planning. In addition, underrepresentation of ultra-rare RHDs in coding systems hampers tracing RHD patient pathways and estimating the global number of persons living with RHDs and their access to precise diagnosis and new option for treatments. This untraceable data also limit the long-term sustainability of existing and new patient registries established at both the national and the European levels.

Aiming to cope with this fragmentation of data, the Directive 2011/24/EU on the application of patient rights in cross border healthcare seeks to facilitate access to healthcare for EU citizens and encourage cooperation between EU Member States (MS) in the field of health. In this directive, there is a crucial article regarding the implementation of registries. Accordingly, a number of MS have developed national strategies to keep track of RD patients in the country, including codification and registering of RD patients. The following countries have reported the existence of a national registry established specifically for RD patient cases: Belgium, Bulgaria, France, Italy, Latvia, Slovak Republic, Spain and UK. In addition, national scientific societies support a number of disease specific registries as showed in May 2019 Orphanet Report Series report 'Rare Disease Registries in Europe', there are 753 disease registries in Europe: 69 operate at the European level; 69 Global; 535 National and 80 Regional. Meanwhile, most of the registries are public (83%), 10% are private – for profit and 7% private non-for profit.

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

The European Reference Networks (ERNs) legal framework sets out the objectives, principles and criteria of the ERNs and defines the general implementation process including the assessment, approval and evaluation of the ERNs. Once approved, ERNs are expected to be evaluated every five years. However, Member States (MS), ERNs and European Commission (EC) have identified the need to establish a solid continuous monitoring system of the ERNs to allow a closer follow up of the activities performed by the networks. The process to set up such a monitoring and information system involves a huge challenge both at organisational and technical level including periodical self-assessment and reporting of the activities of the ERNs and Healthcare Providers (HCPs) to the EC and the Board of MS for ERNs.

In this context, ERN Continuous Monitoring Working Group of the Member States and the ERN Coordinators defined 18 Core indicators to be finally agreed by the ERN Board of MS and the ERN Coordinators Group in September 2018, several of them with specific focus the monitoring of two types of ERNs patient population:

- ERNs CPMS population: The patients that due to their complexity or need of expert advice are included in the CPMS
- ERNs total patient population: The aggregated number of patients looked after by each of the HCPs of a given ERN.

While the first one represents the individual patients and treating clinicians that would directly benefit from the expert advice of the ERNs from a cross border perspective, the second one will benefit as well in an indirect way from the improvements in the knowledge, tools and expertise of the HCP that is looking after them with a national perspective.

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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.

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.

EUROPEAN RARE BLOOD DISORDERS PLATFORM (ENROL)

The European Rare Blood Disorders Platform (ENROL), as the European umbrella platform for both new and already existing registries on RHDs, aims at avoiding fragmentation of data by promoting the standards for interoperability of patient registries, released by the EU RD platform. 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 will map at the EU level 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. Target-driven actions will be carried-out in collaboration with EURORDIS for educating patients and families about the benefits of enrolment in such registries, including different cultural and linguistic strategies.

The standardized collection and monitoring of disease specific health care outcomes through the ENROL user-friendly platform will determine how specialized care is delivered, where are the gaps in diagnosis, care or treatment and where best to allocate financial, technical or human resources. Moreover, it will allow promoting research especially for those issues that remain unanswered or sub optimally addressed by the scientific community; furthermore, it will allow promoting clinical trials for new drugs. ENROL will enable the generation of evidence for better healthcare for RHD patients in EU as ultimate goal.

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 have a first estimation of the patients population within ERN-EuroBloodNet members
- To conduct a first mapping exercise for the creation of an inventory of EU-RHD registries
- To establish synergies with other ERNs for the implementation of rare disease patients registries

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3. TASKS

TASK 1. ESTIMATION OF THE ERN-EUROBLOODNET MEMBERS ACTIVITY BY NUMBER OF PATIENTS

1.1 RARE HEMATOLOGICAL DISEASES-DISEASE GROUPS (RHD-DG)

ERN-EuroBloodNet disease coverage includes 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. However, some of these entities, especially those of the deeper levels in the classification, can be grouped attending to the expertise and procedures required for the appropriate healthcare provision to patients and the need for its monitoring at national level.

Efforts have been performed for the establishment of Rare Hematological Diseases-Disease Groups (RHD-DG) in order to become the center piece of the ERN-EuroBloodNet central repository for:

- Mapping of experts: disease coverage
- Mapping of patients and highly specialized procedures through members' reporting: number of patients/new patients and number of procedures
- Classify the contents of the website, i.e. Guidelines, educational material.

As detailed in Deliverable 4.1 ERN-EuroBloodNet Repository of Members (February 2020), ERN-EuroBloodNet established a total of 70 RHD-DG, as follows:

- Red blood cell defects: 10 disease groups encompassing 59 disorders
- Bone marrow failure and hematopoietic disorders: 12 disease groups encompassing 42 disorders
- HH and other rare genetic disorders of iron metabolism and heme synthesis: 11 disease groups encompassing 29 disorders
- Rare bleeding-coagulation disorders and related diseases: 9 disease groups encompassing 70 disorders
- Lymphoid malignancies: 19 disease groups encompassing 98 disorders
- Myeloid malignancies: 9 disease groups

RHD-DGs and disorders included under each group are available at Cross Border health section in ERN-EuroBloodNet website, which will be reviewed in the frame of ENROL for their final adoption.

1.2 HARMONIZATION OF ERN-EUROBLOODNET MEMBERS ACTIVITY BY RHD-DG

To the date of the present deliverable the following monitoring exercises have been performed:

- 1st Monitoring exercise: first data collection exercise for the period 2017 – 2018 between January to April 2019.
  - The outcomes of that data collection were presented in the meeting of the Board of 25 June 2019 and showed some validity issues, broad variability and lack of information for some of the indicators. It was agreed to further clarify and improve the definition of some of the indicators.
  - The WG on monitoring produced an updated indicators document including further clarifications and examples after an exhaustive review of the definitions of the indicators including an extensive consultation with all the ERNs. The updated document of definitions was circulated to all the ERNs and published in the webpage in August 2019. Two webinars with the participation of most of the ERNs were also organised by the WG in July and September.
- 2nd Monitoring exercise: Data collection until the month of October 2019 to:
  - Review and complete the 2018 data already included in the system (or pending for some networks)
  - Collect the data corresponding to the first semester of 2019 (all indicators mandatory but three optional that can be reported in January 2020 for the whole year 2019).
- 3rd Monitoring exercise: Data collection ongoing until the month of March 2020 to:
  - Review and complete the 2019 semester 1 data included in the system
  - Collect data for 2019 semester 2
  - Collect the indicators optional to be reported for the whole year 2019

ERN-EuroBloodNet monitoring exercises are performed by the coordination team based on the conduction of an excel template among 66 members representatives and substitutes. During the first monitoring exercise, the excel template prepared for the reporting included the following data request concerting the number of patients:

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- Total number of patients: Section 10 of the Membership Application form "Number of patients with the rare or complex disease(s), condition(s) or highly specialised intervention(s) seen by the Healthcare Provider each year." These numbers represent the total number of patients seen for all the subnetworks covered by the healthcare provider each year, divided into adults and children. The template already included:
    - Data submitted in 2016 for the ERN-EuroBloodNet membership application
    - New cells to be filled for years 2016, 2017 and 2018
    - Information on patients' codification used in the healthcare provider
- Patients by disease: Section 11 of the Membership Application form "Number of patients managed by the healthcare provider as required by the Network to maintain or improve expertise and experience in the rare or complex disease(s), condition(s)." The template already included:
    - Data submitted in 2016 for the ERN-EuroBloodNet membership application regarding a) number of patients/year by diseases, b) number of new patients/year by diseases.
    - New cells to be filled for years 2016, 2017 and 2018

This template has been used in each of the exercises conducted for the update/expansion of the data requested in each period. However, the reporting methodology used so far presents some limitations related to the overall analysis of the data gathered in terms of harmonization of the number of patients provided per disease. 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 RHD-DG is required in order to better understand the picture of the current situation of RHD number of patients within the network.

In addition, the ERN-EuroBloodNet inventory of members and experts is currently being upgraded to allow the direct reporting of the number of patients by RDH-DG by the members through a dedicated application form available in their profiles, avoiding the monitoring via excels files. For full details, see Deliverable 4.1 ERN-EuroBloodNet Repository of Members (February 2020).

TASK 2. EXPLORATORY EXERCISE FOR THE CREATION OF AN INVENTORY OF EU-RHD-REGISTRIES

During the first year of ERN-EuroBloodNet implementation, an analysis of the state of the art of existing registries for rare anaemia disorders (RADs), was performed based in two main complimentary approaches:

a) A brief questionnaire was conducted to create the list of National/European and international registries for RAs - of 33 registries were gathered from the activity: 25 for RBC subnetwork, 4 for BMF subnetwork, 3 for RADs and 1 for RHDs.

b) The report "Rare Disease Registries in Europe" published by Orphanet in May 2017 was analysed in order to compile all the existing registries for RAs already identified by Orphanet - 30 registries were identified addressing RAs, including according to the codes, 56 different entities.

As result of both approaches, a final list of National/European and international registries on RADs 55 registries, 33 from the online survey, 21 registries from the ORPHA report (after removing duplications) and 1 from desk research, including information from 15 European countries. The methodological approach and detailed results are available at Deliverable 7 (SGA2016 – 769064).

Based on the List of National/European and international registries on RADs created during the first year of ERN-EuroBloodNet implementation, a first exploratory exercise on existing registries for RHD has been performed for a) update the RADs registries identified and b) expand to all the RHD. The exploratory exercise has been updated/completed with:

- "Rare Disease Registries in Europe" published by Orphanet in May 2019
- Feedback from ERN-EuroBloodNet members in the 3rd Board of Network meeting held in Barcelona (November 2019), where a parallel session focused on registries was devoted to ask to the attendance divided into their area of expertise the following questions:
    - For which rare diseases or their treatments (for example, BMT) do you consider that needs are the most important for setting up a registry?
    - What type of registry (population-based, hospital-based, Natural History, research…)?
    - Do you contribute to national or European registries on RHD?
        - Role in the governance
        - Metadata and policy for sharing data
    - Do you know if there is a National registry on RD in your country?
    - Are you able to get the data from your Hospital Electronic Health Records? What Codification scheme is used (ICD, ORPHA…)? What would you need from your Hospital?

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TASK 3. ESTABLISHMENT OF SYNERGIES WITH THE ERNS ON RARE CANCERS FOR ERNS REGISTRIES IMPLEMENTATION

Synergies among the existing 24 European Reference Networks (ERNs) are essential in order to joint efforts towards the removal of existing data challenges in the field of RD. Thus, strong collaborations among all ERNs registry initiatives will be ensured through the active participation in the ERN Registries Task Force and through the European Joint Programme on Rare Diseases (EJP-RD), especially towards achieving semantic RD registry interoperability.

In the context of ENROL, special liaisons are envisaged with those ERNs sharing with ERN-EuroBloodNet the coverage of rare cancers: ERN on rare adult solid cancers (ERN-EURACAN), the ERN on paediatric cancer (ERN PaedCan) and the ERN on rare genetic tumour risk syndromes (ERN-Genturis) for addressing the particularities of rare cancers.

In this context, ERN-EuroBloodNet participated in the Kick off of the ERN-EURACAN registry (STARTER) held online the 27th May 2020, where some synergies were fruitfully identified even prior the official start of ENROL.

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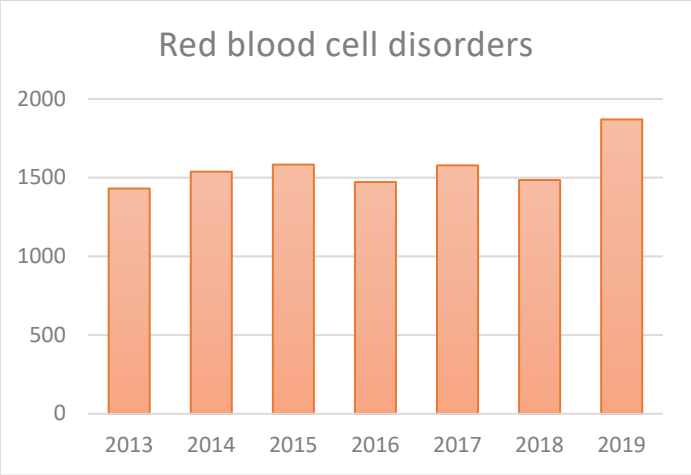
4. RESULTS

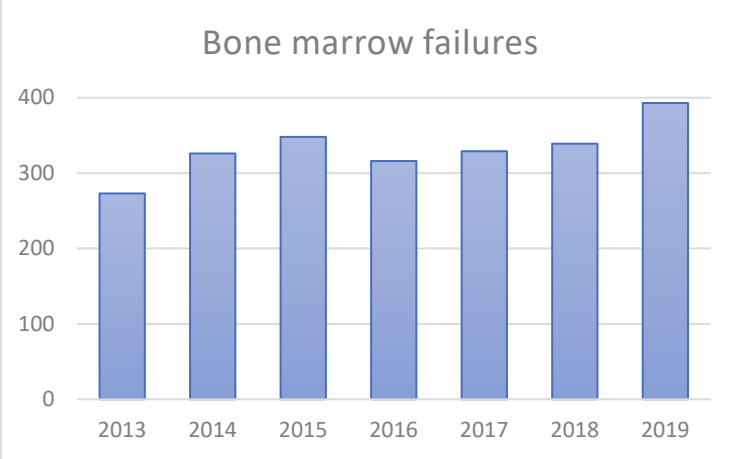
LINKED TO TASK 1. ESTIMATION OF THE ERN-EUROBLOODNET MEMBERS ACTIVITY BY NUMBER OF PATIENTS

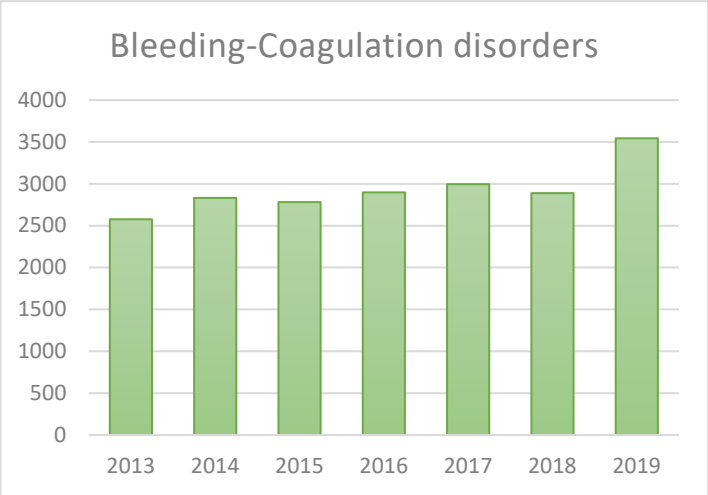
1.1 ANALYSIS OF NUMBER OF PATIENTS REPORTED BY ERN-EUROBLOODNET MEMBERS PER SUBNETWORKS

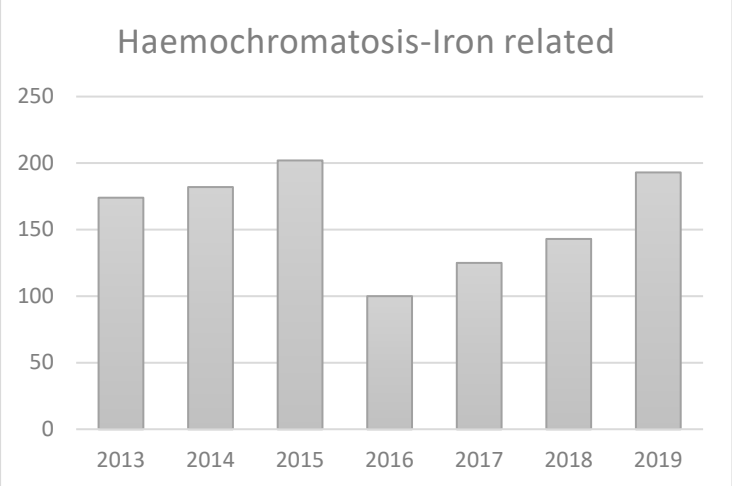
In order to move steps forward a harmonization on the data gathered by the ERN-EuroBloodNet members participation in the monitoring exercises, the number of patients compiled to date has been reviewed and grouped by subnetwork in order to be subclasified by RHD-DG once they are reviewed in the frame of ENROL implementation.

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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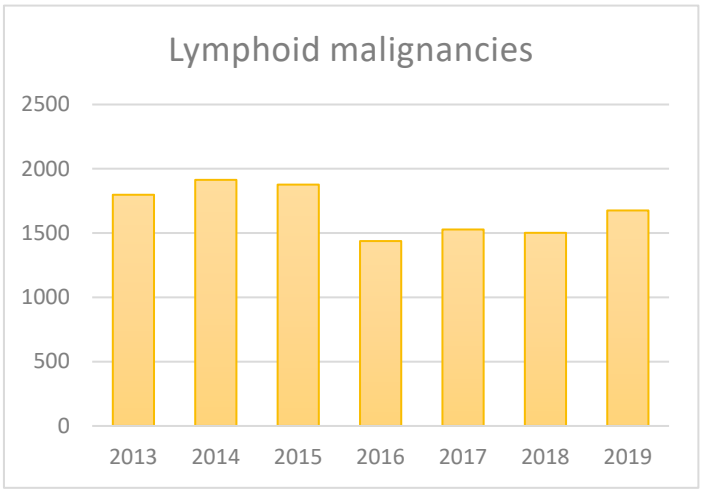
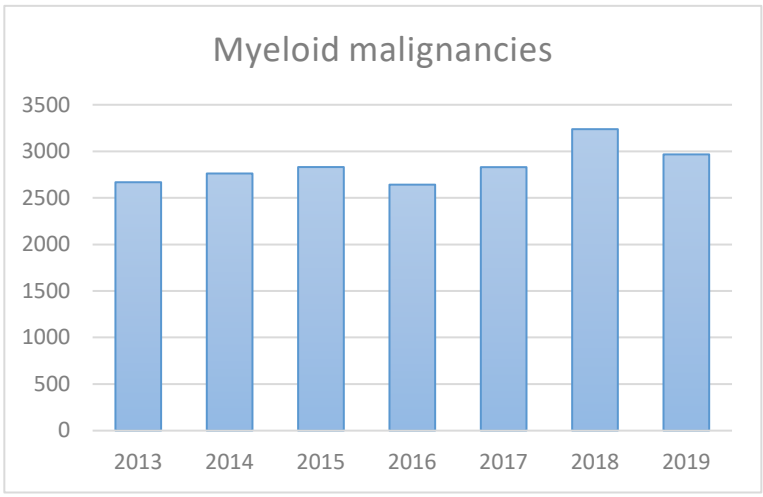
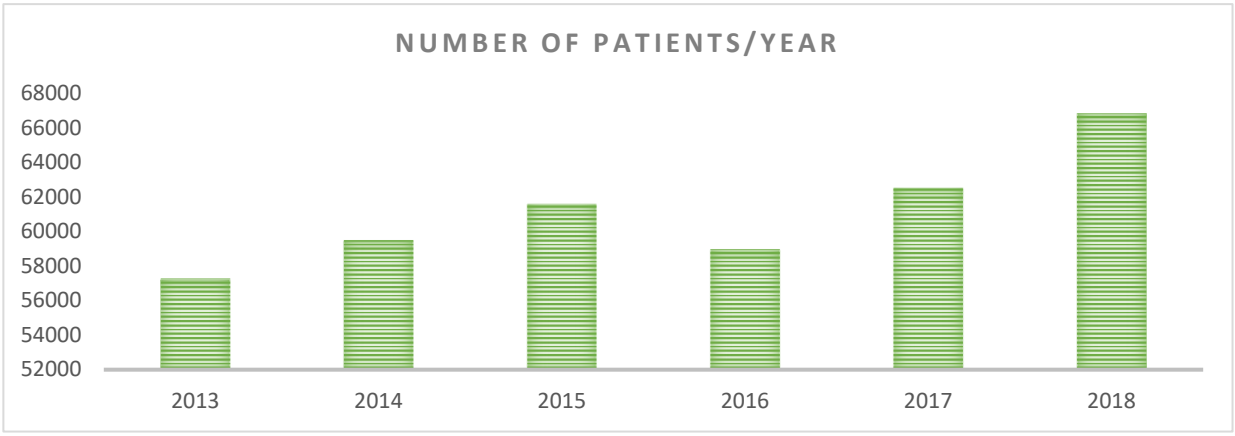




Figures 1-6. Number of new patients per year by subnetwork.

The total number of patients / year and the number of new patients/ year can be found in the Figs. 7-8. Fig. 7 does not include number of patients for year 2019, since data was reported in two semesters, and the participation on both exercises was not equal, reason why its analysis goes beyond a summation on the two semesters and require a deeper analysis.



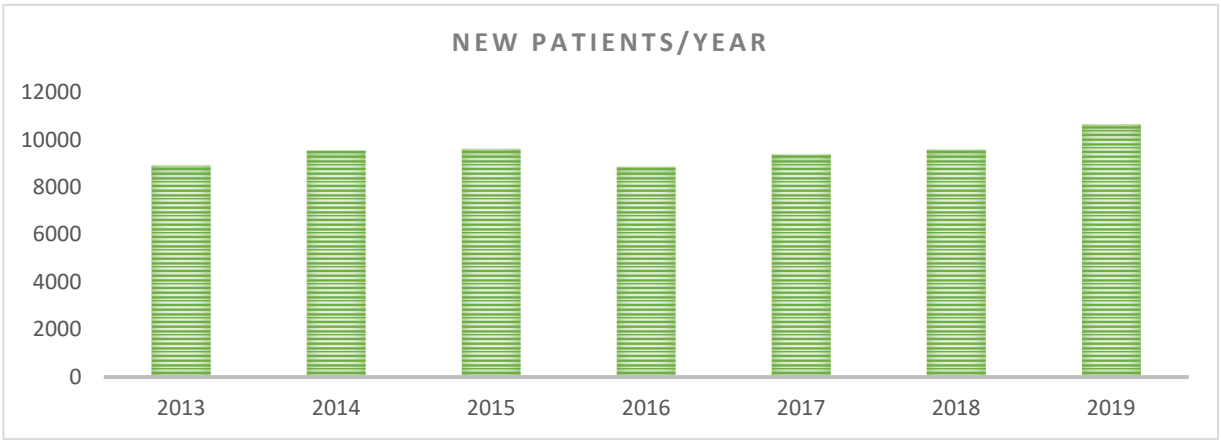


Fig. 7 and 8. Number of patients and New patients per year gathered from ERN-EuroBloodNet membership proposals and monitoring exercises.

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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. 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).

Nevertheless, we would like to emphasize that the participation of ERN-EuroBloodNet members in the monitoring is increasing on each exercise, achieving a total of 90,9% of participation in 2019. With the implementation of the dedicated tool at ERN-EuroBloodNet for self reporting number of patients on RHD-DGs (see Deliverable 4.1 ERN-EuroBloodNet Repository of Members (February 2020)) the number and comparability of data is expected to increase considerably.

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.

Linked to Task 2. Exploratory exercise for the creation of an Inventory of EU-RHD-Registries

After updating the list of National/European and international registries of RADs and expand it RHD the exploratory exercise has allowed the identification of a total 184 registries, including the following disease coverage and geographical scope detailed in Figs. 9 and 10.

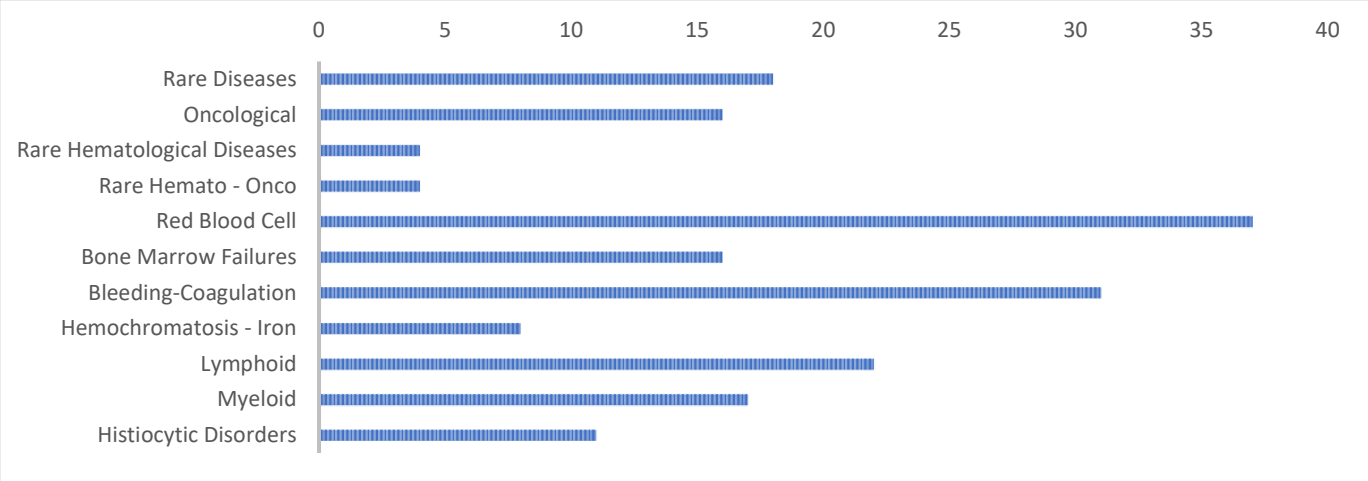

Fig. 9 Number of registries identified and areas covered.

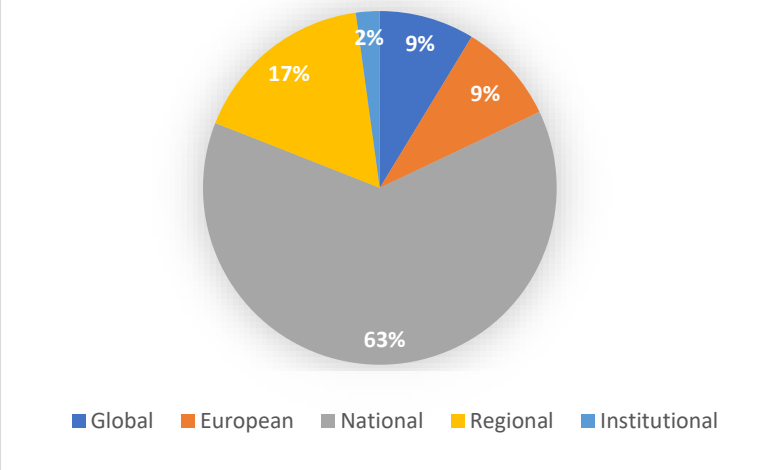

Fig 10. Geographical scope of the registries identified

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The panorama on the Global, European, National or regional existing initiatives vary considerably when tackling oncological or non-oncological RHD (Fig. 11)

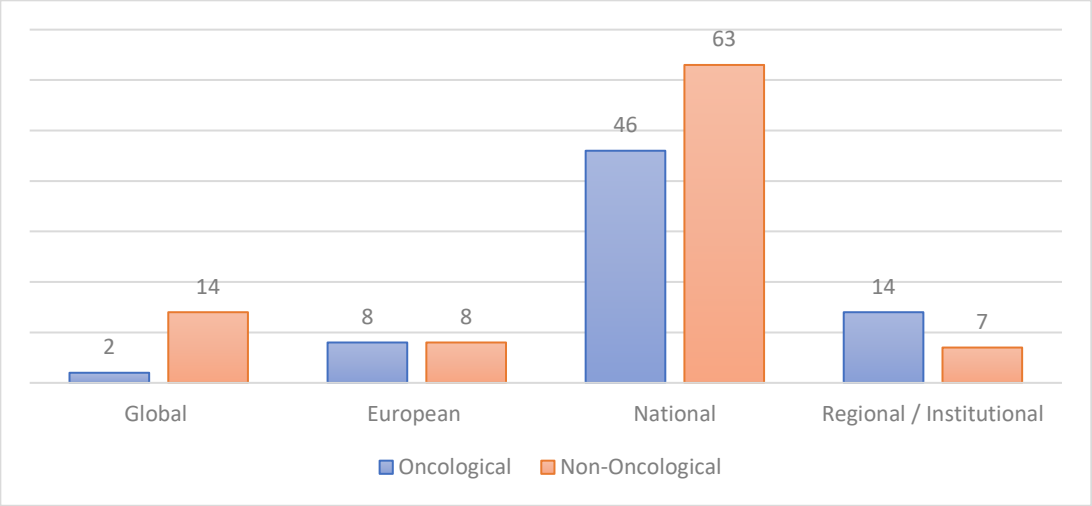

Fig 11. Global, European, National or regional existing initiatives on oncological and non-oncological RHD

When it comes to oncological RHD, some relevant initiatives aims to bridge the gap between clinical research and public health information systems, as HAEMACARE project on oncological RHD as part of EUROCARE, http://www.eurocare.it/. The latter being a collaborative research project on cancer survival in Europe with the participation of a large number of population-based Cancer Registries throughout Europe. More recently, the HARMONY Alliance was established as a public-private European Network of Excellence; its mission is to unlock and spread valuable knowledge on hematologic malignancies among a large number of stakeholders and its goal is to harness and mine Big Data to speed up the development of improved treatments and more effective treatment strategies. Other related initiative is MDS-RIGHT (https://mds-europe.eu/right) for MyeloDysplastic Syndromes, which endorses the European MDS Registry (www.eumds.org) including prospective, observational data on >2,000 lower-risk MDS patients from 16 EU countries + Israel. Other examples of European initiative includes Euro-Histio-Net (https://www.eurohistio.net) for Histiocytic disorders. However, some ultra-rare oncological RHD, as cutaneous lymphomas are not addressed by these initiatives.

Focusing on the national initiatives for the coverage of oncological RHD, 7 national cancer registries have been identified contributing to RARECARE project (Austria, Finland, Iceland, Malta, Norway, Slovakia, Slovenia). Moreover, 19 national registries covering different types lymphoid malignancies have been listed from 8 countries (Austria, Czech Republic, France, Germany, Netherlands, Spain, Sweden, UK), 12 registries on myeloid malignancies on 7 countries (Austria, Bulgaria, Czech Republic, France, Germany, Italy, Spain) and 8 registries covering Histiocytic Disorders in 6 countries (Belgium, France, Germany, Italy, Spain, UK).

In the field of non-oncological RHD, some international initiatives for bleeding disorders include the PedNet Haemophilia registry and PRO-RBDD. The PedNet Haemophilia registry, https://pednet.eu/registry/, is a collaborative effort of the European PEDiatric NETwork for haemophilia management. The registry was set up in 2004 by PedNet investigators to promote and facilitate research and healthcare development in children with haemophilia. At this moment, 31 Haemophilia Treatment centres (HTCs) from 18 countries, a majority of European countries, are collaborating. PRO-RBDD, http://eu.rbdd.org/, is an international collaborating network that has developed a web database designed to prospectively collect clinical and laboratory data of patients with coagulation factor deficiencies in order to evaluate prevalence, bleeding frequency and management, as well as consumption of treatment products and related complications. European initiatives for RADs registries include RADeep (https://www.radeepnetwork.eu). It aims to deal with fragmentation at the EU level for RADs and to link other initiatives like those for aplastic anaemia disorders and their existing registries like the International Fanconi Anemia registry.

On the national initiatives tackling non-oncological diseases, 20 national registries were identified covering bleeding-coagulation disorders from 9 countries (Austria, Belgium, Czech Republic, France, Germany, Italy, Serbia, Spain, UK), 26 covering red blood cell disorders in 12 countries (Belgium, Bulgaria, Czech Republic, Denmark, France, Germany, Ireland, Italy, Netherlands, Spain, Sweden, UK), 14 registries for bone marrow failures in 7 countries (Czech Republic, Germany, Greece, Italy, Netherlands, Spain, UK) and 3 registries on haemochromatosis and iron metabolism related disorders in 3 countries (France, Netherlands, Norway).

Finally, it is important to highlight the European initiative for blood and marrow transplantation: EBMT (https://www.ebmt.org/)

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In the frame of ENROL it is important to stress the identification of the 16 Global and 17 European initiatives found as key potential contacts to establish collaborations and become ENROL data providers. The coverage of these initiatives can be found in Fig. 12.

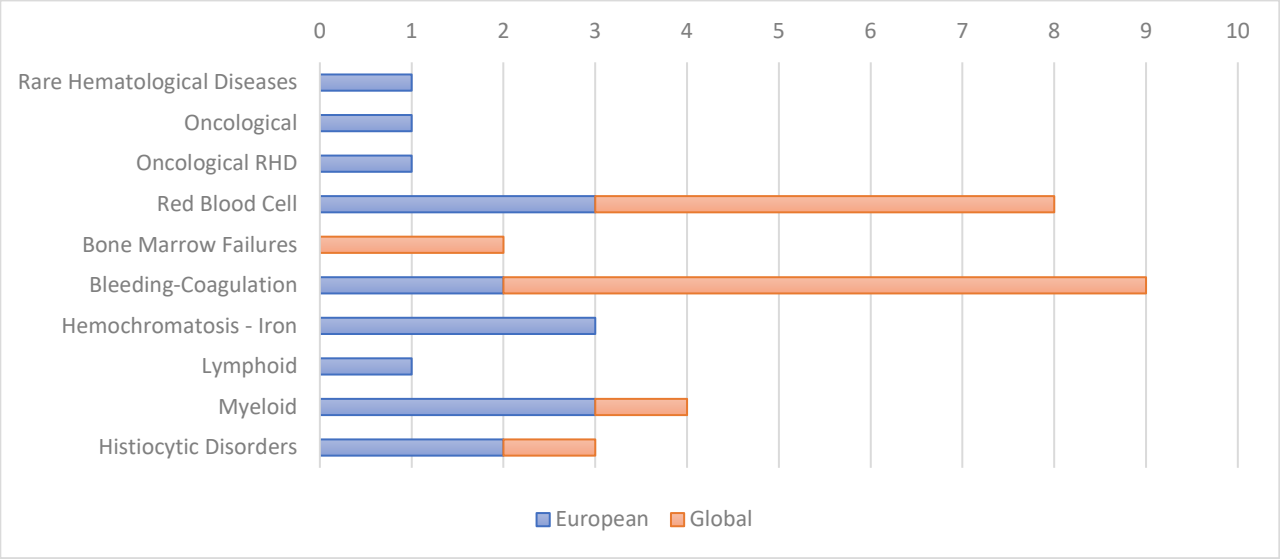

Fig 12. Number of European and Global initiatives per area

On the other hand, the countries with national/regional registries or, the countries coordinating European and Global registries has been summarized in Fig. 13.

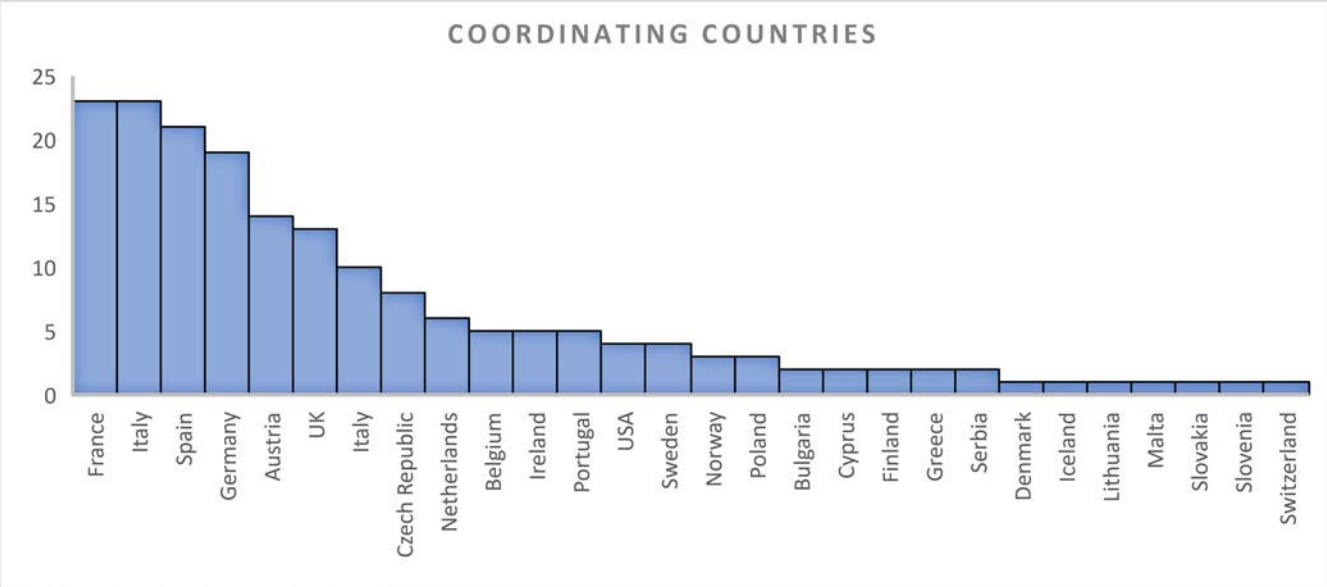

Fig 13. Countries with national/regional registries or coordinating European and Global registries

This analysis has allowed to get the European countries missing from having a national/regional: Croatia, Estonia, Hungary, Latvia, Luxembourg, and Romania. These countries will be approached in order to assess if they are willing to initiate a regional/national registry within the frame of ENROL.

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Lastly, the Public, Private non-for profit and Private for profit nature of the registries have been identified for 121 of the 184 registries identified (Fig. 14).

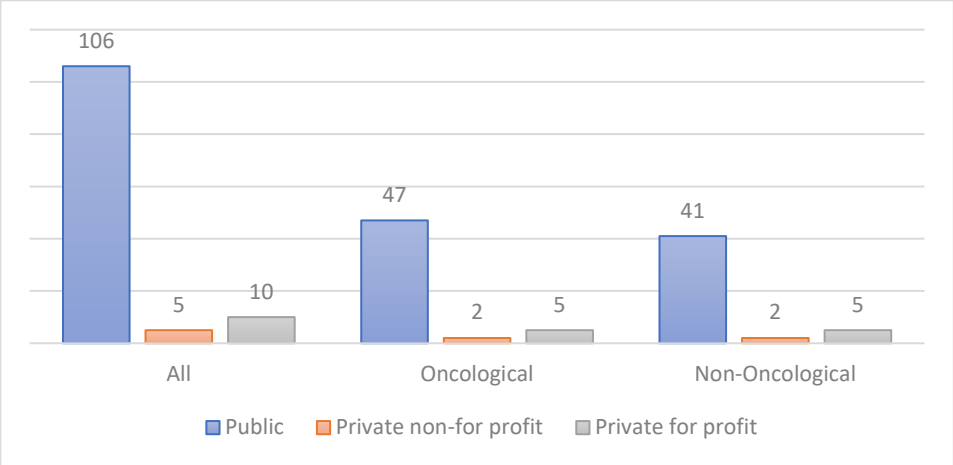

Fig 14. Public, Private non-for profit and Private for profit nature of the registries

From this analysis, the public nature of the vast majority of the registries identified can be easily appreciated in comparison with the private for and non for profit nature initiatives.

LINKED TO TASK 3. ESTABLISHMENT OF SYNERGIES WITH THE ERNS ON RARE CANCERS FOR ERNS REGISTRIES IMPLEMENTATION

The participation of ERN-EuroBloodNet together with ERN-Paedcan and ERN-Genturis in STARTER kick off meeting (central registry of ERN-EURACAN) provided a great opportunity to see specific points where synergies can be actively established. In concrete, in the frame of STARTER-ENROL, the following points for collaboration are under discussion:

- A collaboration is being analysed for joining efforts to conduct a survey among those National/European registries identified and ERN-EuroBloodNet/EURACAN members and affiliated partners to assess their level of FAIRification. Synergies will allow to provide an overview of the members shared among both ERNs and boost the outcomes from the action for global picture on the possibilities for interoperability.
- Joint approach of Ethics committees from participating shared members for their engagement in definition of the Informed Consent.
- Analyse the collaboration on shared cancers
- Governance model and role of patients representatives
- Sharing of data with third parties

In addition, following a proposal from EC - Joint Research Centre (JRC) suggested by Simona Martin and Andri Papadopoulou, an agreement from the ERNs on rare cancers was reached for the establishment of a task force for the definition of a set of Common Data Elements on oncological diseases which will facilitate the gathering of a minimum set of harmonized and structured data on rare cancer patients to contribute to the robustness of evidence compiled.

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5. EXPECTED OUTCOMES & NEXT STEPS

ERN-EuroBloodNet have grouped more than 400 RHDs into 70 disease or disease groups (RHD-DG) for becoming the center piece of a) the members' reporting of number of patients and new patients, b) make the expertise in ERN-EuroBloodNet searchable and c) classify the contents of the website, i.e. Guidelines, educational material. The upgrade performed in the ERN-EuroBloodNet repository of members and experts will allow the direct reporting of members activity on number of patients by RHD-DG, facilitating their contribution to the RHD patients population monitoring.

The first analysis of the RHD population in ERN-EuroBloodNet members 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 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. In this context, the setting up of RHD-DG also will facilitate the definition of ENROL set of common data elements for RHD, RHD-CDE, which will be defined expanding the 16 common data elements for RD registration released by the EU-RD-Platform. Thus, contributing to the Domain specific Common Data Elements (DCDE) on haematological disorders (Proposal by the EJP-RD for semantic RDs registry interoperability). RHD-CDE will incorporate additional elements for patients' stratification according to severity (i.e. chronic blood transfusion) and treatment options (i.e. Bone marrow transplant).

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. This preliminary list will be expanded and validated by the ENROL experts committee in order to create the definitive inventory of registries that will be invited to become data providers of the platform. For those registries interested in participate, an assessment will be performed in terms of technical interoperability and legal and ethical issues. Additionally, registries will be classified according to RHDs disease grouping and countries coverage, setting as the basis for analysing GAPs on existing patients' registries for concrete groups of RHDs and/or in specific Member States.

Also as important remark in the context of interoperability and FAIRification among data sources, collaborations have already been established among all ERNs covering rare cancers (EuroBloodNet, EURACAN, PaedCan and Genturis) and JRC for the establishment of a task force endorsed on the definition of a set of common data elements for rare cancers. Moreover other promising synergies with ERNs on rare cancers have already been identified and will be developed in the frame of ERNs patients registries.

ENROL online Kick off meeting will take place 2nd July 2020, aiming to present the frame and main objectives of ENROL in the context of rare diseases and ERNs. The meeting will count with the participation of ERN-EuroBloodNet members, affiliated partners, and other stakeholders which contribution will be crucial for ENROL implementation and success, as other ERNs representatives and Simona Martin and Andri Papadopoulou from the EC - Joint Research Centre.

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

www.eurobloodnet.eu

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