Deliverable 7

Report on existing registries for RHD

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1-Background and rationale

1.1 Current situation of registries in the context of Rare Diseases

Between 27 and 36 million people are estimated to be living with a rare disease (RD)in the EU. A RD is defined according to the European legislation as a condition presenting a prevalence threshold of not more than five affected persons per 10,000 individuals (Regulation (EC) N°141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products). There exist between 6,000 and 8,000 RD. Lack of access to correct diagnosis or delay in diagnosis is commonly present in RD. In addition, RD research poses challenges to investigators requiring specific approaches to: a) the design of clinical studies; b) the funding of research programs; c) the discovery, testing, and approval of new treatments, and d) the training of clinical scientists. A key element for successful diagnosis, treatment and research of RDs is the availability of exhaustive patient information contained in registries.

Patient registries are key instruments to promote the development of clinical research in the field of RD, and to improve patient care and healthcare planning. They are the only way to pool data in order to achieve a sufficient sample size for epidemiological and/or clinical research. They are crucial to assess the feasibility of clinical trials, to facilitate the planning of appropriate clinical trials and to support the enrolment of patients as well as for the post-marketing surveillance of orphan medicinal products. The creation of a registry can be a powerful tool to create and structure networks of experts, whether they being European Reference Networks of Centres of Expertise or national expert networks for RD. In either case, the experts and centres of expertise involved are a primary source of data for registries.

However, no uniform, accepted standards govern the collection, organization, or availability of these data, and often more than one registry exists for the same rare disease and information has been gathered for decades in a scattered and fragmented way in 600-1000 registries at national, regional, and local levels. At the same time, one estimate is that registries exist for only 20% of rare diseases. A complete list of the existing 600 rare diseases registers in Europe can be found in the Orphanet Report - Disease Registries in Europe – May 2017.

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 clinical, epidemiological, pharmacological trials or other types of research.

The scarcity of relevant knowledge and experience with rarest diseases creates a unique need for cooperation and infrastructure. Support is needed for research initiatives that aim to better understand the distribution and determinants of these diseases and to develop new therapies and other interventions. Innovations in genetics, molecular and computational biology, and other technological advances in basic research are rapidly evolving; however, translating this progress into clinic research and securing governmental or private funding in early stages remains challenging. Some of these challenges can be addressed efficiently through a systematic collection of clinical, genetic, and biologic data in the form of longitudinal patient registries and other coordinated data sources.

The use of observational data methods, including prospective long-term patient registries, is a critical tool in building a broad and comprehensive knowledge base for these often heterogeneous diseases. Important data include the prevalence and distribution of these diseases and key patient, familial, and disease characteristics, including the natural history of the disease. Although many of the basic concepts around registry planning, design, and implementation are directly applicable these disease registries, RD pose some unique challenges. The range of stakeholders for RD is inherently different, which has a direct effect on implementation, governance, funding, communication and as well as their level of interest and willingness to participate in the study of rare diseases. Clinicians with relevant expertise and direct exposure to managing these patients are limited necessitating a broad outreach to identify and recruit enough patients to understand the epidemiology and natural history of the disease. In addition, because of knowledge gaps, the scope and objectives of RD registries are often broader than in a typical disease registry. The absence of standards of care or treatment guidelines in many cases, the common use of experimental therapies, and the incomplete understanding of how these conditions should be monitored in the absence of established or widely accessible biomarkers provide opportunities for RD registries to set the agenda for disease research. Since amassing a sizable population from which any patterns of rare diseases can be discerned is more difficult, novel approaches are often required to both define rare diseases and their relevant outcomes (in other words, scientifically validated and accepted criteria may not exist). Lastly, patient advocacy and support groups are smaller for these often less well-known diseases and may play different roles than in a more traditional disease registry.

1.2 EU position: The European Platform on Rare Diseases Registrarion (EU RD Platform)

The EU has recommended that Member States (MS) should consider supporting at all appropriate levels, including the Community level, on the one hand, specific disease information networks and, on the other hand, for epidemiological purposes, registries and databases, whilst being aware of an independent governance. (Council Recommendation on an action in the field of rare diseases (2009/C 151/02)

The strategical objective of the European Commission is the creation of a European Platform on Rare Diseases Registration providing common services and tools for the existing (and future) rare diseases registries in the European Union.

The European Platform on Rare Diseases Registration (EU RD Platform), being developed by the JRC in collaboration with DG SANTE, aims to cope with the enormous fragmentation of data. It will provide EU-level solutions for data collection and data sharing. The need to access patient health information and data from different places will result in a major boost of the use in electronic data processing within the health system. As a consequence, the implementation of technological solutions allowing both the collection and exchange of patient data within registry networks will be facilitated.

A platform for RD registries, not only fulfils one of the indications of the Council Recommendation on RD, but could also support in several ways the development of the new EU system of rare disease care envisaged by the EU Directive on Cross-Border Health Care. Indeed, the core function of a technological service platform, supporting the collection and sharing of patient data within networks of professionals dedicated to specific diseases, will result in the promotion of clinical research on rare diseases and in greater networking among EU countries and possibly beyond. Actually, the European Platform could even represent an opportunity for networking neighboring Countries.

Up to now, two European central registries are part of the EU RD Platform: the JRC-EUROCAT (European Surveillance of Congenital Anomalies) Central Registry and the JRC-SCPE Central Registry (Surveillance of Cerebral Palsy in Europe, combining 31 SCPE registries from 21 countries) and this guarantees their sustainability. They provide tailor-made datasets for scientific research. The first studies are undergoing in the fields of epidemiology of congenital cerebral anomalies in Europe, effects of early antenatal care on pregnancy outcomes and child health and the prevalence of trisomy 21 at birth.

1.3 Epidemiological data for Rare anaemias: gaps and needs

Due to complications of the disease but also of the treatment, Rare Anaemias (RAs) become over time multi-organ disorders, requiring the involvement of several medical and paramedical specialties. This creates an important burden in the health systems that require monitoring of trends allowing shaping policies aiming to ensure the cost effective allocation of resources.

However, health authorities cannot proceed with the development of services without reliable epidemiological information through patient registries. In the case of RAs, this is particularly important since expertise cannot be made available in every health unit with very small numbers of patients. Thus, a system of expert centres and networks with peripheral services are envisaged as means to provide routine patient care close to their place of residence along with specialised care from a distant reference centre, through either electronic communication or periodic patient visits for specialised tests and consultations. Moreover, patients move frequently for business or pleasure across the EU and a registry aids in protecting each patient by keeping track of his/her situation and needs in order to deliver the right care in every country he/she will be.

Epidemiological data of high quality are also important for engage research and clinical trials because they can direct researchers to the available and suitable patient groups. Basic clinical information is required to describe the clinical status of patients that can comply with the inclusion criteria for a clinical trial, and on the other hand, other patients can be excluded if a registry is well-designed. Registries provide summary data that can be expanded and modified for specific research objectives.

Many unmet needs are present in RAs, especially the haemoglobinopathies and enzyme disorders, with only a single drug currently available in clinical practice as disease modulator (hydroxiurea for SCD). Numbers of patients are rarely adequate in one centre or one country and, hence, pooling of patients in many countries is necessary, as proven by recently conducted trials. However, as in other rare diseases, there are no patients' registries or exhaustive epidemiological studies hampering the development of collaborative research projects and/or clinical trials. The lack of sufficient information on the natural history of the diseases or of specific organ complications with high impact on health care and quality of life hampers the research of new drugs that can prevent complications or cure symptoms and diseases. Therefore, a European approach for the standardized collection of data regarding the main clinical complications of RAs is fundamental to establish the need and the priorities in the

development of clinical trials. By definition an efficient registry is the best tool to put into contact the patient of any rare disease and basic research, both from industry and academia, with reciprocal advantages in terms of generation and access to high quality clinical trials.

On the other hand, there is a number of unmet research needs in the field of RAs leading to a lack of robust evidence based and thus hampering the translation of findings into clinical practice. RAs are characterized for presenting anemia as the main clinical manifestation. In haemolytic anaemias, namely haemoglobinopathies, enzymopathies and membranopathies, anemia results from a loss of red blood cells (haemolysis) mainly in the spleen compensated by an increase of the red blood cell production in the bone marrow (erythropoiesis). The balance between haemolysis and erythopoiesis will determinate the level of anaemia, being a major player in the clinical severity. Common symptomatic treatments include regular red blood cell transfusions and splenectomy. Meanwhile, the only curative treatment is the stem cells transplantation. Gene therapy is still limited to clinical trials. Research on druggable targets modulating the balance between haemolysis and erythropoiesis resulting in an increase Hb concentration will benefit every severe form of RAs. Accordingly, research on new treatment options and/or development of clinical trials could be planned covering several RAs groups, thus increasing the target group and the robustness of evidence base.

Regarding RAs diagnosis, methods for haemoglobinopathies are well established and wide implemented in a harmonized way, however when it comes to less frequent RAs, as enzymopathies, diagnosis tests are not always available even at the national level, and there is a lack of consensus methodology, guidelines and external quality assessment. This leads to a delay in the time of patients' diagnosis and increase the number of undiagnosed or missdiagnosed patients. Thus, underestimating the number of patients and difficulting their adequate treatment and follow-up.

A European approach for the standardised collection of data regarding the main clinical complications of RAs is fundamental to establish the need and the priorities in the development of research projects and clinical trials. By definition, an efficient registry is the best tool to put into contact the patient of any rare disease and basic research, both from industry and academia, with reciprocal advantages in terms of generation and access to high quality clinical trials.

1.4 The Rare Anaemias Disorders European Epidemiological Platform (RADeep)

RADeep, the Rare Anaemia Disorders European Epidemiological Platform, is being implemented as a joint venture conceived in the core of ERN-EuroBloodNet, the European reference network for rare hematological disorders, as an umbrella for both new and already existing European patients' registries in rare anaemias (RAs).

RADeep's implementation is foreseen in different phases through disease specific arms. For eachdisease specific arm, a scientific committee will be established including experts on theprevention, diagnosis and clinical care of the disease, researchers, and national coordinatorsfor data collection.

Ensuring interoperability with European structures fostering research; RADeep will allow mapping at the European level the diagnosis methods, demography, survival rate, main clinical features and treatments of RA patients in order to improve access to specialized and adequate health care and facilitate research and development of new treatments, thus increasing the knowledge and promoting best practices across EU.

Over the last decades, a large number of electronic health records (EHR) have been implemented across EU with the application of several different approaches. Making the existing registries interoperable is a major challenge and will directly lead to the exploitation of available data for research and epidemiological surveillance. In this context and based on the type of data, different codification schemes are currently used for the data entry, e.g. SNOMED for clinical trials, ICD for diseases, HPO for human phenotypes and OMIM for human genes and genetic disorders and trait. Despite the creation of different schemes to enable codification of many diverse fields and parameters, there are still gaps that remain uncovered by existing codification schemes. In addition, the updating of codification schemes has led to disparities between different versions and, thus, to the generation of highly valuable, yet inhomogeneous, data. In order to achieve the FAIRification (make data Findable, Accessible, Interoperable and Reusable) of available data recorded in the health care providers within EuroBloodNet, this project will address these issues, leading to the harmonisation of existing schemes in the case of RAs.

2-Objectives

ERN-EuroBloodNet established five specific objectives as priorities to be accomplished in the frame of the 5 years of implementation, including the specific objective 5: Foster European cooperation in highly specialized procedures for diagnosis, innovative treatments and research

This objective aims to contribute to the EHA roadmap for European Hematology Research by supporting the creation of a European patient registry in RHD, promoting the access to clinical trials, facilitating the provision of –omics platforms and new technologies and fostering research projects in druggable targets identification, gene therapy and pathophysiology.

In line with the specific objective 5, three specific goals were defined to be accomplished in the first year:

1) To start collaboration with already existing databases on RHD for the establishment of a GeoCode surveillance system for ultra-rare RHDs
2) To search for potential third parties interested in stimulating research on diagnosis and treatment for RHDs and exploring on-going clinical trials.
3) To establish a common framework for research programme in collaboration with the EHA roadmap for European Hematology Research.

In relation with objective 1 "To start collaboration with already existing databases on RHD for the establishment of a GeoCode surveillance system for ultra-rare RHDs", the present deliverable describes the methodology defined for the creation of the inventory of existing registries on RHDs.

3-Methods

3.1 Transversal Field of Action on Clinical Trials and Research

The implementation of the ERN-EuroBloodNet action plan has been assured through the establishment of five Transversal Fields of Action (TFAs) in line with each specific objective of the network. In this context, the TFA on Clinical Trials and Research was established aiming to implement all tasks and activities related to the achievement of the specific objective 5.

3.2 Action plan for the first year of ERN-EuroBloodNet implementation

In the context of the TFA on Clinical trials and research in relation with the fostering European surveillance on RHD, the following subtask was foreseen under the 1st year Action Plan:

Task 1. To facilitate European epidemiological surveillance of RHD by promoting the creation of a European registry of patients affected by a RHD

Hematological diseases involve a large group of disorders resulting from quantitative or qualitative abnormalities of blood cells, lymphoid organs and coagulation factors, generally divided in about 6 groups of oncological or non-oncological diseases. With the possible exception of diffuse B cell large cell lymphoma, classical myeloma and chronic lymphocytic leukemia, hematological diseases are rare ORPHA97992, including rare anemias ORPHA 108997, rare coagulation disorders ORPHA 98429, polycythemia ORPHA 98427, and myeloid and lymphoid tumors ORPHA 68347. Rare hereditary hemochromatosis ORPHA220489 was also included in our network following a request from well-established patient groups and experts. As a result, up to 454 different medical entities according to ORPHA codification are covered by ERN-EuroBloodNet, from which 132 are classified as RA and split in 4 different subnetworks:

- Rare Red Blood Cell (RBC) defects, 61 disorders classified as RA
- Bone marrow failure (BMF) and hematopoietic disorders, 46 disorders classified as RA
- Rare bleeding-coagulation disorders and related diseases, 9 disorders classified as RA
- Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis, 16 disorders classified as RA

Taking advantage of the current implementation of RADeep platform, as the future umbrella for both existing and new registries on RAs, and taking into consideration that RAs encompasses four of the six subnetworks of ERN-EuroBloodNet, it was agreed to produce within the present deliverable the state of the art of existing registries for RAs in collaboration with RADeep, joining

efforts towards the achievement of a high quality epidemiological surveillance of RAs as common goal. This step becomes the starting point of the task to be later expanded to the rest of RHD covered by the network.

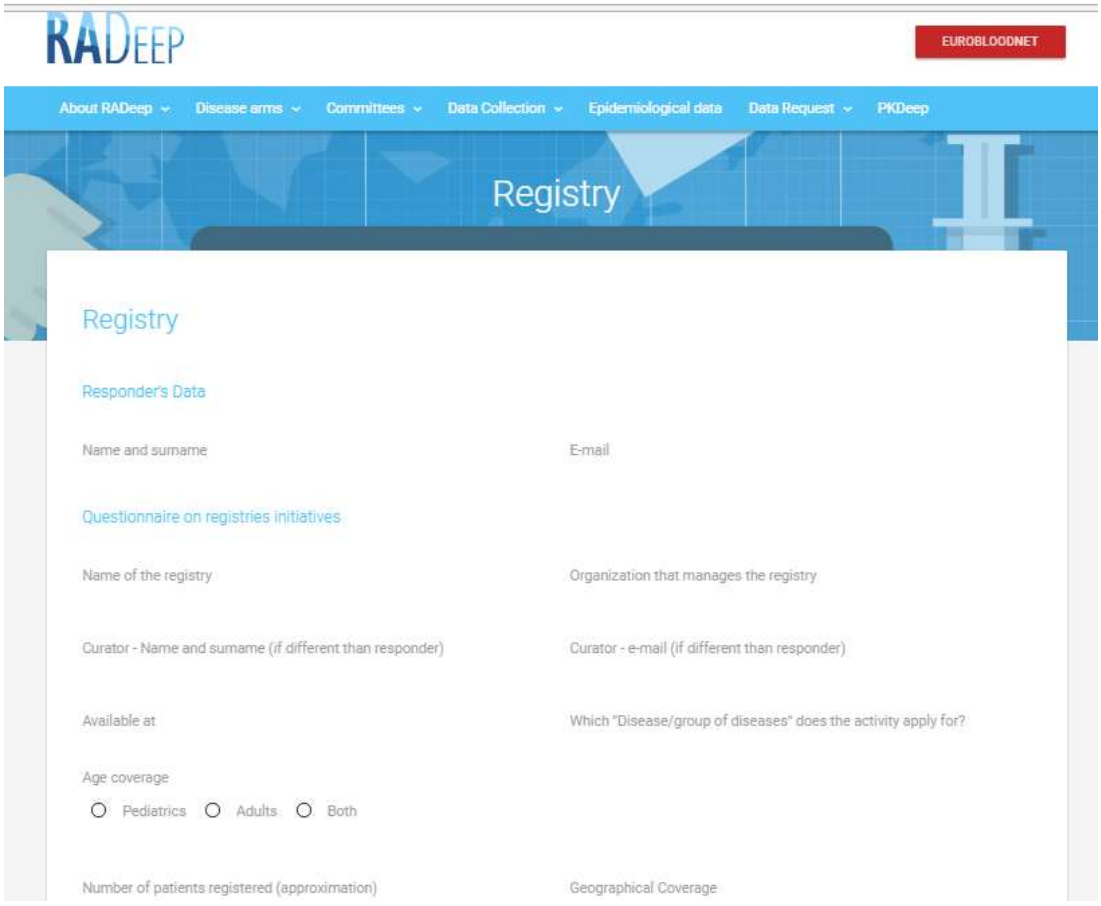
Accordingly, a protocol for the creation of the inventory of existing registries on RAs was designed and agreed based on 2 approaches: a) Survey conducted through ERN-EuroBloodNet website and b) Desk research methodology.

4-Activities implemented

The protocol established for the creation of the repository of existing registries on RAs aiming at creating of a list of National/European and international registries for the RAs, is based in two main complimentary approaches:

4.1 Survey conducted through ERN-EuroBloodNet website

In order to create the list of National/European and international registries for RAs, a brief questionnaire was implemented in ERN-EuroBloodNet website at the specific RADeep's section (https://eurobloodnet.eu/radeep/registry) on December 2017-January 2018.



ERN-EuroBloodNet members were requested to complete the registry's data either they were leading an already established (or in progress) registry for any group of RAs or they participate or know about any registry covering this field. Members also are allowed to forward the link to the curator. The data requested in the questionnaire is the following:

- Responder's Data
    - Name and surname
    - E-mail

- Questionnaire on registries initiatives
    - Name of the registry
    - Organization that manages the registry
    - Curator - Name and surname (if different than responder)
    - Curator - e-mail (if different than responder)
    - Available at
    - Which "Disease/group of diseases" does the activity apply for?
    - Age coverage: Pediatrics Adults Both
    - Number of patients registered (approximation)
    - Geographical Coverage

4.2 Desk research

In parallel, the list created in task 4.1 was consolidated through a desk research undertaken by the coordination based on:

- Orphanet Documents and website.
- Search on PubMed, Google.

5-Results

5.1 Survey conducted through ERN-EuroBloodNet website

After analyzing results obtained from the survey conducted and removing duplications among the answers collected, a total of 33 registries were gathered from the activity: 25 for RBC subnetwork, 4 for BMF subnetwork, 3 for RAs and 1 for RHDs.

Remarkably, from the 33 registries, 27 of them have a national coverage.

5.2 Orphanet database

The report "Rare Disease Registries in Europe" published by Orphanet in May 2017 (http://www.orpha.net/orphacom/cahiers/docs/GB/Registries.pdf) was analysed in order to compile all the existing registries for RAs already identified by Orphanet.

In total 30 registries have been identified addressing RAs, including according to the codes, 56 different entities as shown below:

Subnetwork	Disorders classified as RAs	Disorders covered by identified registries
Rare Red Blood Cell (RBC) defects	61	30
Bone marrow failure (BMF) and hematopoietic disorders	46	16
Rare bleeding-coagulation disorders and related diseases	9	9
Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis	16	1
	132	56

The following classification shows the coverage of the registries involved in the epidemiological surveillance of RAs classified by subnetworks, where the darker colors indicate registries that state their coverage only for that given diseases.

Rare Red Blood Cell (RBC) defects

ORPHA	Group of disease	ORPHA	Group of diseases/diseases	ORPHA	Group of diseases/diseases	ORPHA	Group of diseases/diseases	ORPHA	Group of diseases/diseases
68364	Hemoglobinopathy	2133	Hemoglobin E disease						
68364	Hemoglobinopathy	90039	Hemoglobin D disease						
68364	Hemoglobinopathy	99139	Unstable hemoglobin disease						
68364	Hemoglobinopathy	275745	Alpha-thalassemia and related diseases	846	Alpha-thalassemia	93616	Hemoglobin H disease		
68364	Hemoglobinopathy	275745	Alpha-thalassemia and related diseases	846	Alpha-thalassemia	163596	Hb Bart's hydrops fetalis		
68364	Hemoglobinopathy	275745	Alpha-thalassemia and related diseases	232288	Alpha-thalassemia-related diseases	847	Alpha-thalassemia-X-linked intellectual disability syndrome		
68364	Hemoglobinopathy	275745	Alpha-thalassemia and related diseases	232288	Alpha-thalassemia-related diseases	98791	Alpha-thalassemia-intellectual disability syndrome linked to chromosome 16		
68364	Hemoglobinopathy	275745	Alpha-thalassemia and related diseases	232288	Alpha-thalassemia-related diseases	231401	Alpha-thalassemia-myelodysplastic syndrome		
68364	Hemoglobinopathy	275749	Beta-thalassemia and related diseases	848	Beta-thalassemia	231214	Beta-thalassemia major		
68364	Hemoglobinopathy	275749	Beta-thalassemia and related diseases	848	Beta-thalassemia	231222	Beta-thalassemia intermedia		
68364	Hemoglobinopathy	275749	Beta-thalassemia and related diseases	848	Beta-thalassemia	231226	Dominant beta-thalassemia		
68364	Hemoglobinopathy	275749	Beta-thalassemia and related diseases	231230	Beta-thalassemia associated with another hemoglobin anomaly	46532	Hereditary persistence of fetal hemoglobin-beta-thalassemia syndrome		
68364	Hemoglobinopathy	275749	Beta-thalassemia and related diseases	231230	Beta-thalassemia associated with another hemoglobin anomaly	231237	Delta-beta-thalassemia		
68364	Hemoglobinopathy	275749	Beta-thalassemia and related diseases	231230	Beta-thalassemia associated with another hemoglobin anomaly	231242	Hemoglobin C-beta-thalassemia syndrome		
68364	Hemoglobinopathy	275749	Beta-thalassemia and related diseases	231230	Beta-thalassemia associated with another hemoglobin anomaly	231249	Hemoglobin E-beta-thalassemia syndrome		
68364	Hemoglobinopathy	275749	Beta-thalassemia and related diseases	231230	Beta-thalassemia associated with another hemoglobin anomaly	330032	Hemoglobin Lepore-beta-thalassemia syndrome		
68364	Hemoglobinopathy	275749	Beta-thalassemia and related diseases	231386	Beta-thalassemia with other manifestations	231393	Beta-thalassemia-X-linked thrombocytopenia syndrome		
68364	Hemoglobinopathy	275752	Sickle cell disease and related diseases	232	Sickle cell anemia				
68364	Hemoglobinopathy	275752	Sickle cell disease and related diseases	251355	Sickle cell disease associated with an other hemoglobin anomaly	251359	Sickle cell-beta-thalassemia disease syndrome		
68364	Hemoglobinopathy	275752	Sickle cell disease and related diseases	251355	Sickle cell disease associated with an other hemoglobin anomaly	251365	Sickle cell-hemoglobin C disease syndrome		
68364	Hemoglobinopathy	275752	Sickle cell disease and related diseases	251355	Sickle cell disease associated with an other hemoglobin anomaly	251370	Sickle cell-hemoglobin D disease syndrome		
68364	Hemoglobinopathy	275752	Sickle cell disease and related diseases	251355	Sickle cell disease associated with an other hemoglobin anomaly	251375	Sickle cell-hemoglobin E disease syndrome		
68364	Hemoglobinopathy	275752	Sickle cell disease and related diseases	251355	Sickle cell disease associated with an other hemoglobin anomaly	251380	Hereditary persistence of fetal hemoglobin-sickle cell disease syndrome		
68364	Hemoglobinopathy	280615	Hemoglobinopathy Toms River						
68364	Hemoglobinopathy	621	Hereditary methemoglobinemia						
68364	Hemoglobinopathy	2132	Hemoglobin C disease						
68364	Hemoglobinopathy	330041	Hemoglobin M disease						
68364	Hemoglobinopathy	464453	Acquired methemoglobinemia						
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	98369	Rare constitutional hemolytic anemia due to an enzyme disorder	98372	Hemolytic anemia due to a disorder of glycolytic enzymes	371	Glycogen storage disease due to muscle phosphofructokinase deficiency
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	98369	Rare constitutional hemolytic anemia due to an enzyme disorder	98372	Hemolytic anemia due to a disorder of glycolytic enzymes	713	Glycogen storage disease due to phosphoglycerate kinase 1 deficiency
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	98364	Rare constitutional hemolytic anemia due to a red cell membrane anomaly	822	Hereditary spherocytosis		
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	98364	Rare constitutional hemolytic anemia due to a red cell membrane anomaly	288	Hereditary elliptocytosis		
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	98364	Rare constitutional hemolytic anemia due to a red cell membrane anomaly	93610	Distal renal tubular acidosis with anemia		
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	98364	Rare constitutional hemolytic anemia due to a red cell membrane anomaly	98365	Hereditary stomatocytosis	3203	Overhydrated hereditary stomatocytosis
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	98364	Rare constitutional hemolytic anemia due to a red cell membrane anomaly	98365	Hereditary stomatocytosis	3202	Dehydrated hereditary stomatocytosis
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	98364	Rare constitutional hemolytic anemia due to a red cell membrane anomaly	98365	Hereditary stomatocytosis	71275	Rh deficiency syndrome
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	98364	Rare constitutional hemolytic anemia due to a red cell membrane anomaly	98365	Hereditary stomatocytosis	90044	Familial pseudohyperkalemia
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	98364	Rare constitutional hemolytic anemia due to a red cell membrane anomaly	98365	Hereditary stomatocytosis	98868	Southeast Asian ovalocytosis
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	98364	Rare constitutional hemolytic anemia due to a red cell membrane anomaly	98365	Hereditary stomatocytosis	168577	Hereditary cryohydrocytosis with reduced stomatin
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	98364	Rare constitutional hemolytic anemia due to a red cell membrane anomaly	98365	Hereditary stomatocytosis	398088	Hereditary cryohydrocytosis with normal stomatin
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	98364	Rare constitutional hemolytic anemia due to a red cell membrane anomaly	98366	Constitutional hemolytic anemia due to acanthocytosis	14	Abetalipoproteinemia
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	98364	Rare constitutional hemolytic anemia due to a red cell membrane anomaly	98366	Constitutional hemolytic anemia due to acanthocytosis	59306	McLeod neuroacanthocytosis syndrome
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	98364	Rare constitutional hemolytic anemia due to a red cell membrane anomaly	169464	Primary CD59 deficiency		
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	98369	Rare constitutional hemolytic anemia due to an enzyme disorder	79277	Congenital erythropoietic porphyria		
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	98369	Rare constitutional hemolytic anemia due to an enzyme disorder	98370	Hemolytic anemia due to hexose monophosphate shunt and glutathione metabolism anomalies	32	Glutathione synthetase deficiency
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	98369	Rare constitutional hemolytic anemia due to an enzyme disorder	98370	Hemolytic anemia due to hexose monophosphate shunt and glutathione metabolism anomalies	32	Glutathione synthetase deficiency
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	98369	Rare constitutional hemolytic anemia due to an enzyme disorder	98370	Hemolytic anemia due to hexose monophosphate shunt and glutathione metabolism anomalies	33574	Gamma-glutamylcysteine synthetase deficiency
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	98369	Rare constitutional hemolytic anemia due to an enzyme disorder	98370	Hemolytic anemia due to hexose monophosphate shunt and glutathione metabolism anomalies	90030	Hemolytic anemia due to glutathione reductase deficiency
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	98369	Rare constitutional hemolytic anemia due to an enzyme disorder	98370	Hemolytic anemia due to hexose monophosphate shunt and glutathione metabolism anomalies	99135	6-phosphogluconate dehydrogenase deficiency
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	98369	Rare constitutional hemolytic anemia due to an enzyme disorder	98372	Hemolytic anemia due to a disorder of glycolytic enzymes	868	Triose phosphate-isomerase deficiency
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	98369	Rare constitutional hemolytic anemia due to an enzyme disorder	98372	Hemolytic anemia due to a disorder of glycolytic enzymes	57	Glycogen storage disease due to aldolase A deficiency
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	98369	Rare constitutional hemolytic anemia due to an enzyme disorder	98372	Hemolytic anemia due to a disorder of glycolytic enzymes	766	Hemolytic anemia due to red cell pyruvate kinase deficiency
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	98369	Rare constitutional hemolytic anemia due to an enzyme disorder	98372	Hemolytic anemia due to a disorder of glycolytic enzymes	712	Hemolytic anemia due to glucophosphate isomerase deficiency
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	98369	Rare constitutional hemolytic anemia due to an enzyme disorder	98372	Hemolytic anemia due to a disorder of glycolytic enzymes	714	Hemolytic anemia due to diphosphoglycerate mutase deficiency
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	98369	Rare constitutional hemolytic anemia due to an enzyme disorder	98372	Hemolytic anemia due to a disorder of glycolytic enzymes	90031	Non-spherocytic hemolytic anemia due to hexokinase deficiency
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	98369	Rare constitutional hemolytic anemia due to an enzyme disorder	98372	Hemolytic anemia due to a disorder of glycolytic enzymes	248305	Hemolytic anemia due to glyceraldehyde-3-phosphate dehydrogenase deficiency
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	98369	Rare constitutional hemolytic anemia due to an enzyme disorder	98372	Hemolytic anemia due to a disorder of glycolytic enzymes	466026	Class I glucose-6-phosphate dehydrogenase deficiency
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	98369	Rare constitutional hemolytic anemia due to an enzyme disorder	98374	Hemolytic anemia due to an erythrocyte nucleotide metabolism disorder	35120	Hemolytic anemia due to pyrimidine 5' nucleotidase deficiency
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	98369	Rare constitutional hemolytic anemia due to an enzyme disorder	98374	Hemolytic anemia due to an erythrocyte nucleotide metabolism disorder	86817	Hemolytic anemia due to adenylate kinase deficiency
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	98369	Rare constitutional hemolytic anemia due to an enzyme disorder	98374	Hemolytic anemia due to an erythrocyte nucleotide metabolism disorder	99138	Hemolytic anemia due to erythrocyte adenosine deaminase overproduction
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	178330	Heinz body anemia				

Bone marrow failure (BMF) and hematopoietic disorders

ORPHA	Group of diseases/diseases	ORPHA	Group of diseases/diseases	ORPHA	Group of diseases/diseases	ORPHA	Group of diseases/diseases	ORPHA	Group of diseases/diseases
98363	Rare hemolytic anemia	182047	Rare acquired hemolytic anemia	447	Paroxysmal nocturnal hemoglobinuria				
182040	Aplastic anemia	68383	Rare constitutional aplastic anemia	124	Blackfan-Diamond anemia				
182040	Aplastic anemia	164823	Rare acquired aplastic anemia	447	Paroxysmal nocturnal hemoglobinuria				
182040	Aplastic anemia	68383	Rare constitutional aplastic anemia	811	Shwachman-Diamond syndrome				
182040	Aplastic anemia	164823	Rare acquired aplastic anemia	824	Primary myelofibrosis				
182040	Aplastic anemia	68383	Rare constitutional aplastic anemia	1775	Dyskeratosis congenita				
182040	Aplastic anemia	68383	Rare constitutional aplastic anemia	84	Fanconi anemia				
182040	Aplastic anemia	68383	Rare constitutional aplastic anemia	3088	Revesz syndrome				
182040	Aplastic anemia	68383	Rare constitutional aplastic anemia	3322	Hoyeraal-Hreidarsson syndrome				
182040	Aplastic anemia	68383	Rare constitutional aplastic anemia	3466	WT limb-blood syndrome				
182040	Aplastic anemia	68383	Rare constitutional aplastic anemia	3319	Congenital amegakaryocytic thrombocytopenia				
182040	Aplastic anemia	68383	Rare constitutional aplastic anemia	314399	Autosomal dominant aplasia and myelodysplasia				
182040	Aplastic anemia	68383	Rare constitutional aplastic anemia	397692	Hereditary isolated aplastic anemia				
182040	Aplastic anemia	68383	Rare constitutional aplastic anemia	401764	Pancytopenia-developmental delay syndrome				
182040	Aplastic anemia	164823	Rare acquired aplastic anemia	88	Idiopathic aplastic anemia				
182040	Aplastic anemia	164823	Rare acquired aplastic anemia	98421	Red cell aplasia	98871	Transient erythroblastopenia of childhood		
182040	Aplastic anemia	164823	Rare acquired aplastic anemia	98421	Red cell aplasia	98872	Adult pure red cell aplasia		
182040	Aplastic anemia	68383	Rare constitutional aplastic anemia	228423	Monocytopenia with susceptibility to infections				
182040	Aplastic anemia	68383	Rare constitutional aplastic anemia	71290	Hereditary thrombocytopenia with normal platelets-hematological cancer predisposition syndrome"				
182040	Aplastic anemia	68383	Rare constitutional aplastic anemia	168629	Autosomal thrombocytopenia with normal platelets				
248293	Rare deficiency anemia	248296	Constitutional deficiency anemia	98396	Constitutional megaloblastic anemia due to vitamin B12 metabolism disorder	26	Methylmalonic acidemia with homocystinuria	79282	Methylmalonic acidemia with homocystinuria, type cblC
248293	Rare deficiency anemia	248296	Constitutional deficiency anemia	98396	Constitutional megaloblastic anemia due to vitamin B12 metabolism disorder	26	Methylmalonic acidemia with homocystinuria	79283	Methylmalonic acidemia with homocystinuria, type cblD
248293	Rare deficiency anemia	248296	Constitutional deficiency anemia	98396	Constitutional megaloblastic anemia due to vitamin B12 metabolism disorder	26	Methylmalonic acidemia with homocystinuria	79284	Methylmalonic acidemia with homocystinuria type cblF
248293	Rare deficiency anemia	248296	Constitutional deficiency anemia	98396	Constitutional megaloblastic anemia due to vitamin B12 metabolism disorder	26	Methylmalonic acidemia with homocystinuria	369955	Methylmalonic acidemia with homocystinuria, type cblJ
248293	Rare deficiency anemia	248296	Constitutional deficiency anemia	98396	Constitutional megaloblastic anemia due to vitamin B12 metabolism disorder	26	Methylmalonic acidemia with homocystinuria	369962	Methylmalonic acidemia with homocystinuria, type cblX
248293	Rare deficiency anemia	248296	Constitutional deficiency anemia	98396	Constitutional megaloblastic anemia due to vitamin B12 metabolism disorder	622	Homocystinuria without methylmalonic aciduria	2169	Methylcobalamin deficiency type cblE
248293	Rare deficiency anemia	248296	Constitutional deficiency anemia	98396	Constitutional megaloblastic anemia due to vitamin B12 metabolism disorder	622	Homocystinuria without methylmalonic aciduria	2170	Methylcobalamin deficiency type cblG
248293	Rare deficiency anemia	248296	Constitutional deficiency anemia	98408	Constitutional megaloblastic anemia due to folate metabolism disorder	51208	Formiminoglutamic aciduria		
248293	Rare deficiency anemia	248296	Constitutional deficiency anemia	98408	Constitutional megaloblastic anemia due to folate metabolism disorder	319651	Constitutional megaloblastic anemia with severe neurologic disease		
248293	Rare deficiency anemia	248296	Constitutional deficiency anemia	98396	Constitutional megaloblastic anemia due to vitamin B12 metabolism disorder	859	Transcobalamin deficiency		
248293	Rare deficiency anemia	248296	Constitutional deficiency anemia	98396	Constitutional megaloblastic anemia due to vitamin B12 metabolism disorder	332	Congenital intrinsic factor deficiency		
248293	Rare deficiency anemia	248296	Constitutional deficiency anemia	98396	Constitutional megaloblastic anemia due to vitamin B12 metabolism disorder	622	Homocystinuria without methylmalonic aciduria	308380	Methylcobalamin deficiency type cblDv1
248293	Rare deficiency anemia	248296	Constitutional deficiency anemia	98396	Constitutional megaloblastic anemia due to vitamin B12 metabolism disorder	35858	Gräsbeck-Imerslund disease		
248293	Rare deficiency anemia	248296	Constitutional deficiency anemia	98408	Constitutional megaloblastic anemia due to folate metabolism disorder	90045	Hereditary folate malabsorption		
248293	Rare deficiency anemia	248296	Constitutional deficiency anemia	98415	Vitamin B12- and folate-independent constitutional megaloblastic anemia	30	Hereditary orotic aciduria		
248293	Rare deficiency anemia	248296	Constitutional deficiency anemia	98415	Vitamin B12- and folate-independent constitutional megaloblastic anemia	49827	Thiamine-responsive megaloblastic anemia syndrome		
248293	Rare deficiency anemia	248296	Constitutional deficiency anemia	98415	Vitamin B12- and folate-independent constitutional megaloblastic anemia	206428	Hypoxanthine-guanine phosphoribosyltransferase deficiency	510	Lesch-Nyhan syndrome
248293	Rare deficiency anemia	248296	Constitutional deficiency anemia	98415	Vitamin B12- and folate-independent constitutional megaloblastic anemia	206428	Hypoxanthine-guanine phosphoribosyltransferase deficiency	79233	Hypoxanthine guanine phosphoribosyltransferase partial deficiency
293830	Constitutional dyserythropoietic anemia	85	Congenital dyserythropoietic anemia	98873	Congenital dyserythropoietic anemia type II				
293830	Constitutional dyserythropoietic anemia	85	Congenital dyserythropoietic anemia	67044	Thrombocytopenia with congenital dyserythropoietic anemia				
293830	Constitutional dyserythropoietic anemia	85	Congenital dyserythropoietic anemia	98869	Congenital dyserythropoietic anemia type I				
293830	Constitutional dyserythropoietic anemia	85	Congenital dyserythropoietic anemia	98870	Congenital dyserythropoietic anemia type III				
293830	Constitutional dyserythropoietic anemia	85	Congenital dyserythropoietic anemia	293825	Congenital dyserythropoietic anemia type IV				
293830	Constitutional dyserythropoietic anemia	85	Congenital dyserythropoietic anemia	363727	X-linked dyserythropoetic anemia with abnormal platelets and neutropenia				
293830	Constitutional dyserythropoietic anemia	77297	Majeed syndrome						
293830	Constitutional dyserythropoietic anemia	199337	Pancreatic insufficiency-anemia-hyperostosis syndrome						

Rare bleeding-coagulation disorders and related diseases

ORPHA	Group of diseases/diseases	ORPHA	Group of diseases/diseases	ORPHA	Group of diseases/diseases	ORPHA	Group of diseases/diseases
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	2134	Atypical hemolytic-uremic syndrome	357008	Atypical hemolytic-uremic syndrome with DGKE deficiency
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	2134	Atypical hemolytic-uremic syndrome	93575	Atypical hemolytic-uremic syndrome with C3 anomaly
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	2134	Atypical hemolytic-uremic syndrome	93576	Atypical hemolytic-uremic syndrome with MCP/CD46 anomaly
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	2134	Atypical hemolytic-uremic syndrome	93578	Atypical hemolytic-uremic syndrome with B factor anomaly
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	2134	Atypical hemolytic-uremic syndrome	93579	Atypical hemolytic-uremic syndrome with H factor anomaly
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	2134	Atypical hemolytic-uremic syndrome	93580	Atypical hemolytic-uremic syndrome with I factor anomaly
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	2134	Atypical hemolytic-uremic syndrome	93581	Atypical hemolytic-uremic syndrome with anti-factor H antibodies
98363	Rare hemolytic anemia	182043	Rare constitutional hemolytic anemia	2134	Atypical hemolytic-uremic syndrome	217023	Atypical hemolytic-uremic syndrome with thrombomodulin anomaly
98363	Rare hemolytic anemia	182047	Rare acquired hemolytic anemia	90038	Typical hemolytic-uremic syndrome		

Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis

ORPHA	Group of diseases/diseases	ORPHA	Group of diseases/diseases	ORPHA	Group of diseases/diseases	ORPHA	Group of diseases/diseases
1047	Sideroblastic anemia	75564	Acquired idiopathic sideroblastic anemia				
1047	Sideroblastic anemia	98362	Constitutional sideroblastic anemia	699	Pearson syndrome		
1047	Sideroblastic anemia	98362	Constitutional sideroblastic anemia	2598	Mitochondrial myopathy and sideroblastic anemia		
1047	Sideroblastic anemia	98362	Constitutional sideroblastic anemia	2802	X-linked sideroblastic anemia and ataxia		
1047	Sideroblastic anemia	98362	Constitutional sideroblastic anemia	49827	Thiamine-responsive megaloblastic anemia syndrome		
1047	Sideroblastic anemia	98362	Constitutional sideroblastic anemia	75563	X-linked sideroblastic anemia		
1047	Sideroblastic anemia	98362	Constitutional sideroblastic anemia	255132	Adult-onset autosomal recessive sideroblastic anemia		
1047	Sideroblastic anemia	98362	Constitutional sideroblastic anemia	260305	Autosomal recessive sideroblastic anemia		
1047	Sideroblastic anemia	98362	Constitutional sideroblastic anemia	300298	Severe congenital hypochromic anemia with ringed sideroblasts		
1047	Sideroblastic anemia	98362	Constitutional sideroblastic anemia	369861	Congenital sideroblastic anemia-B-cell immunodeficiency-periodic fever-developmental delay syndrome		
248293	Rare deficiency anemia	248296	Constitutional deficiency anemia	98360	Constitutional anemia due to iron metabolism disorder	83642	Microcytic anemia with liver iron overload
248293	Rare deficiency anemia	248296	Constitutional deficiency anemia	98360	Constitutional anemia due to iron metabolism disorder	1195	Congenital atransferrinemia
248293	Rare deficiency anemia	248296	Constitutional deficiency anemia	98360	Constitutional anemia due to iron metabolism disorder	48818	Aceruloplasminemia
248293	Rare deficiency anemia	248296	Constitutional deficiency anemia	98360	Constitutional anemia due to iron metabolism disorder	209981	IRIDA syndrome
248293	Rare deficiency anemia	248296	Constitutional deficiency anemia	98360	Constitutional anemia due to iron metabolism disorder	300298	Severe congenital hypochromic anemia with ringed sideroblasts
248293	Rare deficiency anemia	248302	Rare acquired deficiency anemia	54028	Plummer-Vinson syndrome		

Big differences are appreciated when comparing the coverage of the registries identified to the total of disorders classified as RAs by subnetworks.

For instance, in the case of Rare Red Blood Cell (RBC) defects, approximately half of the disesases are covered by existing registries. It is important to highlight that almost the totally of them are covering most prevalent RBC diseases (hemoglobinopathies), while other diseases less prevalent remain without any umbrella (eg. Enzymopathies, membranopathies). On the other hand there are two diseases covered due to a metabolism disorder (Glycogen storage disease due to muscle phosphofructokinase deficiency and Glycogen storage disease due to phosphoglycerate kinase 1 deficiency). Although one of their clinical manifestation is hemolytic anaemia, these diseases are likely to be covered by registry/registries dedicated to metabolic disorders.

By contrast, it is also remarkable to appreciate the total coverage or the RAs belonging to the Rare bleeding-coagulation disorders. There is a total of 4 Atypical Hemolytic Uremic Syndrome (aHUS) registries, which may be result of the clinical trial for the disease that is currently being implemented.

Nevertheless, some data called our attention when focusing on the coverage of the existing registries. Since information about the data gathered by the registry is introduced by ORPHA codes, some of the registries seem extremely highly specialized. As example, there is one registry covering only sickle cell anaemia, but not other forms of sickle cell disease providing similar clinical manifestations. When noticing similar cases, mistakes in reporting codification of coverage may be taken into consideration.

5.3 List of National/European and international registries on RAs.

As result of both approaches, a final list has been created with the aim to compile the existing registries initiatives and most relevant related information on RAs. This list can be found in Annex I List of National/European and international registries on RAs.

Final list includes a total of 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.

As explained before, one of the major concerns of RDs epidemiology is the fragmentation of data and lack of initiatives at international level to gather a high quality epidemiological surveillance. This is perfectly reflected when focussing on the coverage of this list, where 43 of

the registries have a national coverage while 11 have a global or European. In this context, European umbrellas for the merge of existing data on specific fields provide a solution to this problem.

As a general comment, most of registries do not have official website available to find general information of the registry as diseases covered, legal frame, information for participation... This is specially noticed in national registries.

6-Agreements for GeoCode

In order to estimate the prevalence and incidence of a certain disease, it is essential to have the sufficient evidence based on number of patients correctly diagnosed. This should not be a problem if procedures for diagnosis are well established and harmonized among countries, however ultra rare diseases usually require very specific methodologies for their diagnosis that are only provided by centers of expertise in the field. In this scarced expertise relies one of the main challenges for the ultra rare diseases, which is to correct the underestimation of patients undiagnosed by the achievement of the correct diagnosis through highly specialized methodologies to be translated into the estimation of prevalence and incidence of such diseases.

It is well known that countries with experts trained in the diagnosis of very rare diseases, usually report higher numbers of patients when compared to the rest of countries, even if there is not an ethnic component justifying such variations. The most likely explanations are both differences in the availability of advanced diagnostic procedures and different levels of the awareness for the diagnosis of the diseases. An example of this situation is found on Congenital Dyserythropoietic Anaemia (CDA), where number of patients are much higher in those countries with experts on diagnosis (eg. Italy, France, UK…)

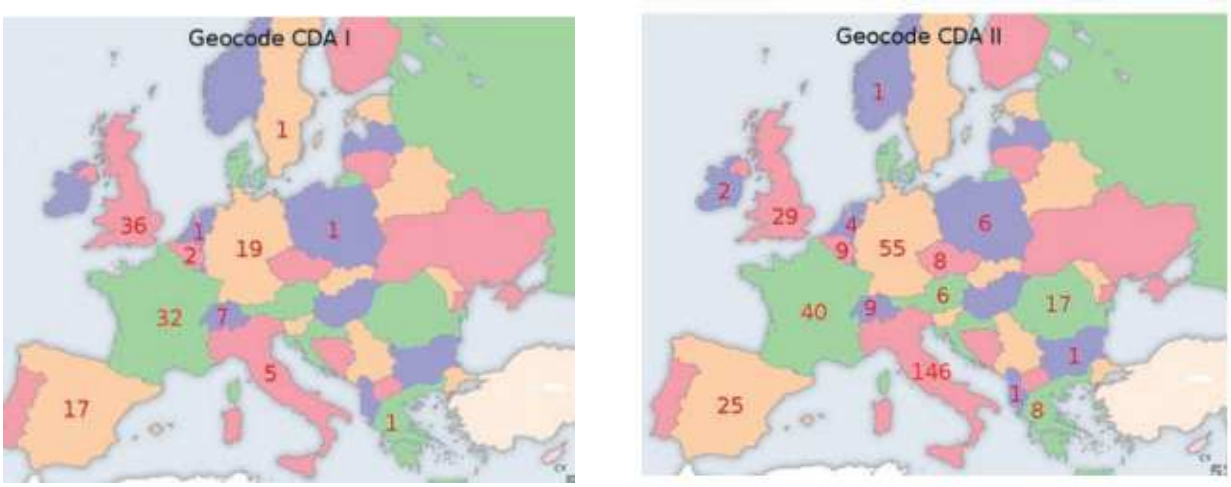


Image 1. Number of cases collected by country. (Source: *Frequency of congenital dyserythropoietic anemias in Europe. Heimpel H. et al. Eur J Haematol. 2010 Jul;85(1):20-5.)*

For these cases where the real number of patients cannot be obtained due to high rates of undiagnosed cases, it is necessary to implement an approach based on total number of patients diagnosed and gathering the methods employed for the diagnosis in each country in order to improve access to diagnosis facilities while reducing the number of undiagnosed cases. GeoCode

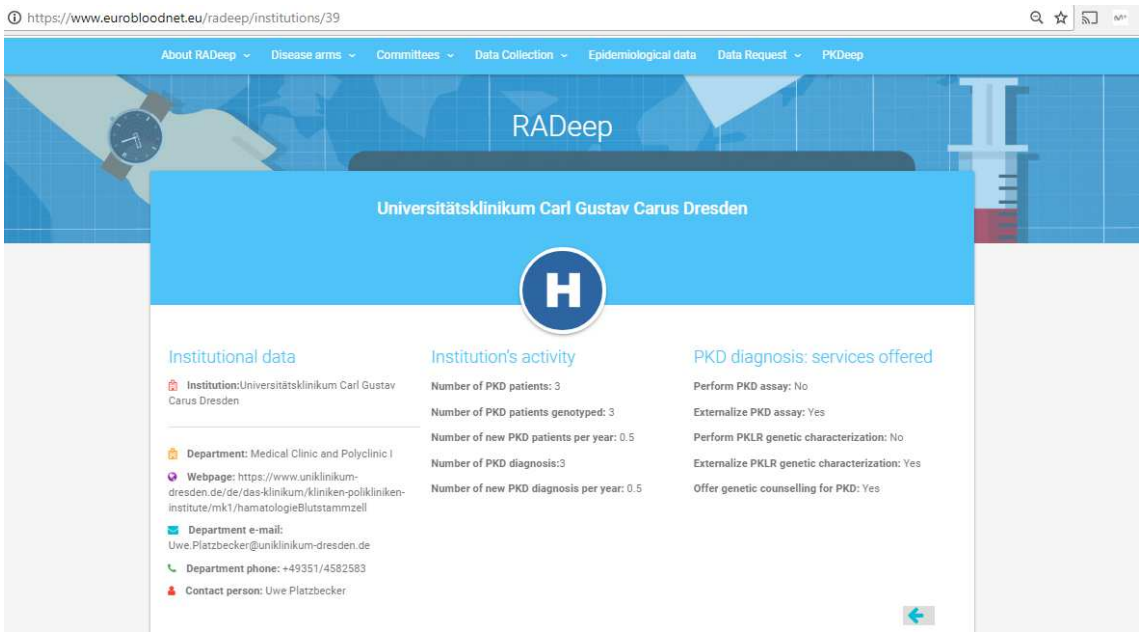
is defined as the system for gathering of both number of patients and methods on diagnosis, in order to have an overview of the situation of the ultra rare diseases.

During first year of implementation of ERN-EuroBloodNet a GeoCode system has been established for the Pyruvate Kinase Deficiency (PKD). An agreement has been established among ERN-EuroBloodNet members dealing with PKD and a scientific committee has been created with this porpoise: https://www.eurobloodnet.eu/radeep/pkdeep

Scientific Board of PKDeep is formed by:

- Wilma Barcellini - Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Italy
- Paola Bianchi - Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Italy
- Maria del Mar Mañú Pereira - University Hospital Vall d'Hebron - Vall d'Hebron Research Institute, Spain
- Serge Pissard - CHU Henri Mondor, France
- Eduard van Beers - University Medical Center Utrecht, The Netherlands
- Richard van Wijk - University Medical Center Utrecht, The Netherlands
- Tabita Magalhaes Maia - Centro Hospitalar e Universitário de Coimbra, Portugal
- Celeste Bento - Centro Hospitalar e Universitário de Coimbra, Portugal

Mapping of methods for diagnosis and number of patients are publicly available at Mapping of facilities section on: https://www.eurobloodnet.eu/radeep/pkdeep



A total of 41 medical centres from 10 countries participated in the mapping of facilities for PKD. 260 PKD patients are currently in follow-up, 231 of them (88,85%) have been genetically characterized. A mean of 25,95 new PKD patients per year would be in follow-up counting all medical centres. Total number of PKD diagnosis is found to be 481, 31,88 new diagnoses per year.

Only seven of the 38 medical centres presented more than 10 patients in follow-up, accounting for 180 of the 260 patients registered and based in France, Italy, Netherlands, Portugal and United Kingdom. However, when adjusting the number of patients in follow-up according to the total population of the country, the highest values are found in France, Netherlands and Portugal, and the lowest in Germany, United Kingdom and Spain.

Regarding percentage of PKD patients genotyped, 88,85% of the patients have been genetically characterized. The lowest values for PKD genotyping are found in Czech Republic, United Kingdom and Spain.

It is important to highlight that answers were received also from two medical centres, one in Bulgaria and one in Cyprus, both of them belonging to ERN-Eurobloodnet as centres of expertise for Red Blood Cell disorders, i.e. haemoglobinopathies. None of them reported any patient affected by PKD or offered any diagnosis facility for PKD. In both cases, PKLR gene characterization is offered in the country but not the PK Activity (based on the answers). In addition, in Bulgaria, PKD diagnosis both phenotypic and genetic is not covered by the national health system, thus is not likely to be performed.

7-Expected outcomes and next steps

7.1. Expected outcomes and next steps

The implementation of the protocol established for the creation of a repository of registries on RAs has shed light on the state of the art on available registries on RAs at national and international level.

As already indicated before, the RADeep Platform will provide the infrastructure to collect and integrate data from existing registries for fostering the gathering of data from available sources. Based on the identified registries and related information, curators will be approached in order to both, establish collaborations within RADeep and include them as scientific board members and/or national coordinators.

Accordingly, as expected outcome, the inventory of existing registries on RAs will become a source of potential members providing data to RADeep. Two methodological approaches for the integration of these registries into the platform will be performed based on the following criteria:

- For more prevalent RAs:
    - National registries for more prevalent RAs as haemoglobinopathies (i.e. for Thalassaemia in Cyprus, France and UK, or for Sickle Cell Disease in UK, Belgium or The Netherlands) have been well-established in some European Member States.
    - If national registries have not been implemented and due to its higher prevalence in comparison to very rare diseases, great number of patients may be found in the Electronic Health Records of some healthcare providers.

In these cases where a high number of patients need to be included into the platform, automatic transfer of data to RADeep will be assessed (individual or aggregated depending of interoperability, registries policies and national regulations).

- For very rare RAs:
    - National registries can be difficultly found for less prevalent RAs, as enzymopathies, membranopathies or congenital dyserythropoietic anaemias.
    - Patients affected by very RAs usually constitute the single case of a healthcare provider and are only registered in the Electronic Health Record of the center or in some registry created as part of a research project if existing.

In these cases where a single or very few numbers of patients need to be introduced into the platform, a manual approach for the transfer of data to RADeep will be assessed (individual or aggregated depending of interoperability, registries policies and national regulations).

In addition, further collaborations are undergoing for the establishment of a GeoCode system for CDA and stomatocytosis.

As final result, the up-to-date and continuous mapping of services and patients across Europe that RADeep will allow in liaisons with research community and industry for the re-use of data will promote development of clinical trials and –OMICS based research on drug-able targets, especially in those countries with limited access to drugs. In addition, it will allow doing exploratory study population queries aiming at identify adequate target populations to include in clinical trials and reach the adequate numbers of patients.

On the other hand, following the methodology established for the other TFAs, during next steps an online questionnaire will be loaded on to the ERN-EuroBloodNet website in order to gather key essential information from the members targeted to existing activities/services/initiatives related to registries, clinical trials and research initiatives, leading to the expansion of the inventory of existing registries to all RHDs. This enlargement will provide valuable information on the situation for the rest of diseases that will be public available at ERN-EuroBloodNet website while promoting their use among health professionals and scientific community and thus, fostering the epidemiological surveillance of RHD at European level.

7.2 Target groups

The expected target audiences that will directly benefit from the exhaustive inventory of existing registries on RHD include:

- Health care professionals dealing with patients affected by RHD that may be interested in contributing to a National/European/international epidemiological initiative.
- Patients and patient organisations willing to participate in an epidemiological health record may find registries covering their disease.
- Biotechnological and pharmaceutical industries may find registry initiatives covering their research/clinical trials area. Thus, the inventory will promote the collaborations among existing registries and industries.

Annex I

List of National/European and international registries on RAs

List of National/European and international registries on Rare Anaemias

Country	Registry title	Disease Coverage	Subnetwork	Patient Age	Patient Number	Geographical Coverage	Link (if available)
Austria	International aHUS registry	Atypical hemolytic uremic syndrome	Bleeding	Both	NA	Global	http://www.ahusregistry.com/index.html?id=%27back%27
Belgium	National Sickle Cell Disease Register	Sickle Cell Disease	RBC	Both	1000	National	https://www.drepano.be/Drepano
Belgium	Central Registry of Rare Diseases	Rare Diseases	RD	Both	NA	National	https://rarediseases.wiv-isp.be/en/registry
Bulgaria	National registry of patients with thalassaemia major	Thalassaemia	RBC	NA	NA	National	https://www.raredis.org/?p=1012&lang=en
Bulgaria	The Bulgarian genetic registry of monogenic disorders	Rare Diseases	RD	NA	NA	National	NA
Cyprus	Cyprus Thalassaemia Patients Registry	Haemoglobinopathies	RBC	Both	1183	National	NA
Finland	Finnish Hematology Register and Biobank - FHRB	Rare Diseases	RHD	Both	NA	National	http://www.fhrb.fi/front-page.html
France	French registry for beta-thalassemia	Beta-thalassemia major and intermedia	RBC	Both	660	National	NA
France	BasePédia Drépa (in elaboration)	Sickle Cell Disease	RBC	Pediatrics	NA	Regional	NA
France	Escort-Hu: European sickle cell disease cohort- hydroxyurea	Sickle Cell Disease	RBC	NA	NA	European	NA
France	CODE-PK	Pyruvate Kinase Deficiency	RBC	Both	NA	National	NA
France	European Society for Blood and Marrow Transplant Society Registry (EBMT registry)	Rare Hematological Diseases	RHD	Both	NA	European	https://www.ebmt.org/Contents/Data-Management/Registrystructure/Pages/Registry-structure.aspx
France	French constitutive hematologic diseases registry	Rare Hematological Diseases	RHD	Both	NA	National	NA
France	French Registry of Atypical Hemolytic Uremic Syndrome (aHUS) in Children	Atypical hemolytic uremic syndrome	Bleeding	Pediatrics	NA	National	NA
Germany	GPOH-Register Sichelzellkrankheit	Sickle Cell Disease	RBC	Pediatrics	250	National	NA
Germany	Fanconi anemia registry	Fanconi anemia	BMF	Both	NA	National	NA
Germany	German central registry for Sickle cell disease and Thalassaemia	Sickle cell disease and Thalassaemia	RBC	Both	NA	National	http://www.uniklinik-duesseldorf.de/unternehmen/kliniken/klinik-fuer-kinder-onkologie-haematologie-und-klinische-immunologie/haematologisch-onkologische-ambulanz-ka04/sichelzellerkrankung-und-thalassaemie
Germany	German paroxysmal nocturnal hemoglobinuria registry	Paroxysmal nocturnal hemoglobinuria	BMF	NA	NA	National	NA
Germany	National registry for Blackfan-Diamond disease	Blackfan-Diamond disease	BMF	NA	NA	National	NA
Ireland	Sickle Cell disease Paediatric Registry	Sickle Cell Disease	RBC	Pediatrics	360	National	NA
Ireland	Membranopathy Paediatric Registry	Red cell membranopathies	RBC	Pediatrics	175	National	NA
Ireland	Enzymopathy Paediatric Registry	Red cell enzymopathies	RBC	Pediatrics	NA	National	NA
Ireland	Thalassaemia major and intermedia Paediatric Registry	Thalassaemia	RBC	Pediatrics	NA	National	NA
Italy	MIOT (Myocardial Iron Overoload in Thalassemia)	Sickle cell disease and Thalassaemia	RBC	Both	2700	National	NA
Italy	Registro Italiano Thalassemie ed altre Emoglobinopatie	Haemoglobinopathies	RBC	Both	NA	National	NA
Italy	DB-INTHEM Italian Network of Hemoglobinopaties	Haemoglobinopathies	RBC	Both	2500	National	NA
Italy	ITALIAN REGISTRY under development	Sickle cell disease and Thalassaemia	RBC	Both	NA	National	NA
Italy	HTA-THAL	Haemoglobinopathies	RBC	Both	1900	National	NA
Italy	Database of RBC enzymopathies	Red cell enzymopathies	RBC	Both	150	Global	NA
Italy	Database of RBC membrane disorders (HS HE HSt)	Red cell membranopathies	RBC	Both	500	National	NA
Italy	Database of congenital dyserythropoietic anemias	Congenital dyserythropoietic anemias	BMF	Both	50	National	NA
Italy	International Health Repository	Thalassaemia	RBC	Both	9671	Global	NA
Italy	Data Base Italiano Anemia di Fanconi	Rare Anemias, Constitutional Marrow Failure	RA	Both	200	National	NA
Italy	International Registry of CDAs	Congenital dyserythropoietic anemias	BMF	Both	250	Global	NA
Italy	International Registry of HST	Hereditary Stomatocytosis	RBC	Both	150	Global	NA
Italy	International registry of recurrent and familial hemolytic uremic syndrome/thrombotic thrombocytopenic purpura	Hemolytic uremic syndrome	Bleeding	NA	NA	Global	http://www.marionegri.it/en_US/home/research_en/ricerca_clinica_en/registri_patologia_en/seu_ppt_registry
Italy	Italian registry of hemolytic uremic syndrome	Hemolytic uremic syndrome	Bleeding	NA	NA	National	http://www.iss.it/seu/index.php?lang=1
Italy	National registry of Rare Diseases	Rare Diseases	RD	NA	NA	National	http://www.iss.it/cnmr/index.php?lang=2&id=991&tipo=53
Italy	RIAF: Fanconi's anemia Italian registry	Fanconi anemia	BMF	NA	NA	National	http://www.airfa.it/page.php?id=8
Lithuania	HESS	Rare Hematological Diseases	RHD	Adults	NA	National	NA
Spain	REPHem REGISTRO ESPAÑOL PEDIÁTRICO DE HEMOGLOBINOPATÍAS	Sickle cell disease and Thalassaemia	RBC	Pediatrics	1200	National	https://www.e-clinical.org/rephem/index.aspx
Spain	aHUS/C3G: Database of atypical hemolytic uremic syndrome and C3 glomerulonephritis	Atypical hemolytic uremic syndrome	Bleeding	NA	NA	National	https://www.ahusc3g.es/register/Pages/Public/Home.aspx
Spain	Fanconi anemia patient registry database	Fanconi anemia	BMF	NA	NA	National	NA
Spain	Spanish registry of rare diseases (ReeR: Spanish National Registry of Rare Diseases)	Rare Diseases	RD	NA	NA	National	https://registroraras.isciii.es/Comun/Inicio.aspx
Sweden	Anemiregistret/Transfusionsregistret	Rare Anemias (specially blood transfusion dependent)	RA	Pediatrics	100	National	NA
Switzerland	Paroxysmal Nocturnal Hemoglobinuria registry	Paroxysmal Nocturnal Hemoglobinuria	BMF	Both	NA	Global	http://www.pnhregistry.com/
The Netherlands	SCORE (Sickle Cell Outcome REsearch)	Sickle Cell Disease	RBC	Both	1750	National	NA
The Netherlands	Dutch Inherited Bone Marrow Failure Registry	Inherited bone marrow failure syndromes	BMF	Both	44	National	NA
The Netherlands	Database of RBC enzymopathies	Red cell enzymopathies	RBC	Both	NA	National	NA
UK	Unexplained Anaemia	All inherited anaemias (DBA, CDA, sideroblastic, membrane, enzymes)	RA	Both	300	National	NA
UK	National Haemoglobinopathy	Sickle cell disease and Thalassaemia	RBC	Both	12000	National	NA
UK	UK National Haemoglobinopathy Registry (NHR)	Sickle cell disease and Thalassaemia	RBC	Both	13000	National	www.nhr.nhs.uk
UK	EHR: European Haemoglobinopathy Registry	Haemoglobinopathies	RBC	NA	NA	European	http://www.sicklecellsociety.org/resources/european-haemoglobinopathy-registry/
UK	UK & Ireland Fanconi Anaemia Registry	Fanconi anemia	BMF	NA	NA	National	NA
USA	PKD NHS	Pyruvate Kinase Deficiency	RBC	Both	250	Global	NA