

## DELIVERABLE 4.2 ERN-EUROBLOODNET REPOSITORY OF MEMBERS

ERN-EuroBloodNet: European Reference Network on Rare Hematological Diseases

EUROPEAN REFERENCE NETWORKS  
FOR RARE, LOW PREVALENCE AND COMPLEX DISEASES

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## DOCUMENT INFORMATION

### DELIVERABLE 4.2 ERN-EUROBLOODNET REPOSITORY OF MEMBERS

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#### Short Description

Report on ERN-EuroBloodNet's members' profiles, including data on the HCPs, experts and multidisciplinary team, diseases covered, and core facilities for health provision. This will be also accessible through EuroBloodNet website

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## 1. INTRODUCTION

### CROSS-BORDER HEALTH IN THE FIELD OF RARE HEMATOLOGICAL DISEASES

As in other Rare Diseases (RDs), expertise in Rare Hematological Diseases (RHDs) is scarce and distributed heterogeneously across the EU and there is no accessible repository of human and technical resources available to challenge the difficulties of RHD at the EU or national levels. As a result many patients suffer either a delay diagnose or remain undiagnosed over time, while it is also well known cases for specific diseases incorrectly diagnosed due to a trend on the awareness of close entities overlapping the clinical manifestations. Thus, many patients are wrongly monitored resulting in an improper delivery of healthcare. In addition, highly specialized procedures for both cure or monitor long term complications including organ damage are not available or fully implemented across EU leading to big inequalities on the access to healthcare.

The Directive 2011/24/EU on Cross-border health provides the keys for the establishment of a referral system for patients and samples in order to ensure the same level of access to healthcare across Europe. However, previous information on the expertise and services available at each MS is mandatory for the identification of needs and the establishment of evidence-based patients and cross-border pathways leading to a best healthcare care for each individual European patient, improvement of health services delivery for RHD across EU and better use of resources.

### ERN-EUROBLOODNET MAPPING OF HIGHLY SPECIALIZED PROCEDURES AND EXPERTISE

#### Highly Specialized Procedures in the context of Rare Hematological Diseases

As the basis for a cross-border health action, we define highly specialized procedures (HSP) as those procedures that for a number of reasons, are not available in all EU-MS, thus preventing the delivery of the best care for EU citizens suffering from a rare haematological disease (RHD) independently of their country of origin. HSP involve both interventions for diagnosis and for treatment, and their complexity can rely on technological advances or expertise of multidisciplinary team, or both.

In this context, during previous period of ERN-EuroBloodNet implementation, the state of the art of Next generation sequencing (NGS) and Bone marrow transplantation (BMT) on non-oncological disorders was analysed as highly specialized procedures key for the diagnosis or treatment of many non-oncological RHD and presenting high inequalities for its access among EU-MS. Two questionnaires were conducted among members with the gathering of 50 and 39 and responses respectively. Answers allowed the identification of important gaps among the need and availability of a) NGS for rare anaemia and b) BMT for Sickle cell disease.

During the 3rd Board of Network meeting, new HSPs potential targets of Cross border health were identified, including: a) Diagnostic procedures, treatment and follow-up of primary intra-ocular lymphomas, and b) Transcranial Doppler for Sickle Cell Disease pediatric patients.

#### Mapping of Experts & Networks enlargement

As starting point for the mapping of experts, an inventory of [ERN-EuroBloodNet inventory of members and experts](#) was created during previous period of the network implementation (2017-2018) for creating a public and accessible repository of the expertise available in the network. ERN-EuroBloodNet inventory is based on Experts, Departments, and Members profiles. Profiles are editable through a set of applications forms allocated in the private area and integrate the ORPHA classification for RHD in its back office, allowing the selection of health professionals' specific area of expertise as well as for the diseases covered. In addition, a [Disease Search tool](#) has been implemented to exploit the data gathered through the inventory, making the expertise available in the network findable and searchable to the public.

From their establishment on 2017, ERNs are currently experiencing the enlargement of the number of types of members of the networks through a) the designation of **Affiliated Partners (APs)**, and b) the launch of the call for **new ERNs members**.

As a result, ERN-EuroBloodNet has increased its coverage with [10 Affiliated Partners from 8 countries](#), and have received a total of 38 applications for new members from 11 countries (Assessment ongoing - Expected date for official membership Q2 2021), therefore an upgrade of the inventory is being implemented for their proper inclusion.

## 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 1: Improve equal access to highly specialized healthcare delivery for RHD across Europe.

Through this activity ERN-EuroBloodNet aims to build a central repository of reliable sources of information on expertise on RHDs available at both national and European level allowing the:

- a) Identification of needs for cross border health actions based on existing gaps in certain MS for clinical management of a specific condition
- b) Establishment of new bridges for collaboration not only among expertise available in ERN-EuroBloodNet members but also with other experts out of the ERN coverage.

In this context, the specific objectives of this deliverable is to show the latest actions and results for:

1) Expansion and upgrade the ERN-EuroBloodNet inventory of members and experts established during previous period of network implementation for:

- Incorporating the new types of ERNs members and ensure their searchability and visibility
- Mapping of ERN-EuroBloodNet expertise and website materials based on an improved structure linked to Rare Hematological Diseases-Disease Groups (RHD-DGs)

2) Mapping availability of HSPs considered as essential for the delivery of best healthcare and thus, defined as priorities for the potential establishment of cross-border pathways.

## 3. TASKS

### TASK 1. ENLARGEMENT OF ERN-EUROBLOODNET REPOSITORY OF EXPERTS

#### TECHNICAL IMPLEMENTATION OF NEW PROFILES

Based on the ERN-EuroBloodNet enlargement of the existing membership, the following health professionals profiles will be differentiated at the repository, including: Full members (current, and the new potential members currently under evaluation) and Affiliated partners.

### TASK 2. RARE HEMATOLOGICAL DISEASES-DISEASE GROUPS

#### RHD-DGs REVISION AND UPDATE

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.

In this context, 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: diseases of expertise
- Classify the contents of the website, i.e. Guidelines, educational material.

With the definition of RHD-DG, two major specificity levels of RHD classification will be available in the ERN-EuroBloodNet inventory of experts and health services:

- a) RHD ORPHA classification "entire": The whole tree classification of ORPHA for RHDs will be available for the Experts to select their specific expertise. Experts are searchable when a very concrete disease is searched in the search tool
- b) RHD classification "Disease groups": The RHD-DG established based on ORPHA/ICD will become the center piece of the website for members' reporting and classification of website contents.

During the previous period of implementation, an analysis of the ORPHA and ICD codification schemes was performed, leading to the definition of a first version of 70 RHD-DGs with the contribution of subnetwork coordinators and other experts in the field (see Deliverable 4.1 ERN-EuroBloodNet Repository of members for further details).

In the present period of implementation, a revision of the RHD-DGs has been performed for its final implementation at the ERN-EuroBloodNet website back office.

### TASK 3. HIGHLY SPECIALIZED PROCEDURES FOR EUROPEAN MAPPING

#### DIAGNOSTIC PROCEDURES, TREATMENT AND FOLLOW-UP OF PRIMARY INTRA-OCULAR LYMPHOMA

Intraocular lymphomas include different types of lymphomas that could involve many parts of the eye. Primary vitreo-retinal lymphoma (PVRL) is a complex disease. The first ocular symptoms and the clinical signs of PVRL could be easily confounded with chronic uveitis, leading to a delay of diagnosis of 1 year on average. The common ophthalmologic examination but also more specific tests could provide a high clinical suspicion of PVRL, however, all of these tests are not available in all care centers and the choice of ones from others depends on the practice of hematologist, neurologist and ophthalmologist.

The main goals of the treatment of PVRL are the management of the intraocular disease but also to prevent, if possible, the apparition of CNS involvement which is responsible of the bad prognosis of the pathology. However, precise guidelines are still lacking, and daily practice differs from team to team. While some teams prefer local treatment only, others teams use systemic treatment and use intravitreal treatments only in case of specific situations. Even the definition of clinical response to treatment or relapse differs between specialists (hematologists, neurologists, ophthalmologists) and between teams.

All in all, the creation of a European task force bringing together different specialists hematologists, neurologists and ophthalmologists could be the optimum approach to face this challenges.

As starting point, ERN-EuroBloodNet has conducted in collaboration with the multidisciplinary team of Institut Curie dealing with PVRL patients, Denis Malaise, Ophthalmologist, Alexandre Matet, Ophthalmologist, Nathalie Cassoux, Ophthalmologist and

Carole Soussain, Hematologist, a European mapping exercise to identify the state of the art of the management of PVRL across Europe and specifically to:

- Identify how these lymphomas are diagnosed, treated and monitored in “real life”
- Assess the necessity of the establishment of a European task force for epidemiological surveillance and the establishment of European guidelines

## **TRANSCRANIAL DOPPLER FOR SICKLE CELL DISEASE PEDIATRIC PATIENTS**

ERN-EuroBloodNet aims to evaluate the availability of Transcranial Doppler (TCD) for children with Sickle Cell Disease (SCD), as a highly specialized procedure required for the adequate management of these patients.

In order to assess the availability and expertise on this HSP across EU, a mapping exercise has been created by the following ERN-EuroBloodNet hematologists experts on SCD pediatric patients: Raffaella Colombatti (AO Padua, Italy), Maddalena Casale (AOU - Second University - Naples, Italy), Daniela Cuzzubbo (Ospedale Pediatrico Meyer Firenze, Italy), Corrina McMahon (Children's Health Ireland, Ireland), Mariane de Montalembert (Assistance Publique-Hôpitaux de Paris, Hôpital Necker-Enfants Malades, France) and Vincenzo Voi (AOU S.Luigi Gonzaga, Italy).

Specifically, the results of this survey will shed light on the availability of TCD in Europe allowing the identification of issues related to the lack of access, lack of training for staff, lack of adequate protocols for implementation of TCD and treatment afterwards, etc, which could be addressed through dedicated actions in the network.



## 4. RESULTS

### LINKED TO TASK 1. ENLARGEMENT OF ERN-EUROBLOODNET REPOSITORY OF EXPERTS

#### TECHNICAL IMPLEMENTATION OF NEW PROFILES

The current structure implemented for the full ERN-EuroBloodNet members, including their dedicated: a) Healthcare provider profile, b) Departments profiles and c) Experts profiles, is being technically upgrading to allow the new representatives and multidisciplinary teams from Affiliated partners and future new members to create the public profiles.

Moreover, the search tool is being upgraded in order to show in a visual-appealing design the different types of profiles matching with the concrete disease of expertise search and/or any other of the filters available in the profiles (ie. patient age coverage, area of expertise, country...).

Upgrades are currently being performed by the Website developers and are expected to be released in Q2 2021.

### LINKED TO TASK 2. RARE HEMATOLOGICAL DISEASES - DISEASE GROUPS

#### RHD-DGs REVISION AND UPDATE

As a result of the revision of the first version, the final list of RHD-DGs include a total of 69 groups, as follows:

- Red blood cell defects: 10 disease groups
- Bone marrow failure and hematopoietic disorders: 9 disease groups
- HH and other rare genetic disorders of iron metabolism and heme synthesis: 12 disease groups
- Rare bleeding-coagulation disorders and related diseases: 9 disease groups
- Lymphoid malignancies: 16 disease groups
- Myeloid malignancies: 12 disease groups
- Histiocytic and dendritic cell neoplasms: 1 disease group

This final version of the RHD-DGs has served as the basis for the upcoming tools and web redesign that has already been provided to the website developers and will be implemented in the next period of implementation. One of the novelties include the “RHD-DGs Disease cards” that will interrelate the different website sections, tools and materials around the RHD-DGs (see 6. Expected outcomes & Next steps for further details).

### LINKED TO TASK 3. HIGHLY SPECIALIZED PROCEDURES FOR EUROPEAN MAPPING

#### DIAGNOSTIC PROCEDURES, TREATMENT AND FOLLOW-UP OF PRIMARY INTRA-OCULAR LYMPHOMA

The mapping exercise was agreed among the expert team from Institute Curie with the following structure:

- The first part of the survey concerns global information about the physician, as the type of hospital (public, private, referential center...) where PVRL are managed.
- Following block of questions are dedicated to the diagnosis of PVRL, with a different approach depending on the specialists (hematologist/neurologist versus ophthalmologist). Precise questions are asked on the type of ophthalmologic examinations requested in case of suspicion of PVRL and which systemic work-out is performed to exclude concomitant CNS involvement. A specific question focusses on cytokine dosage on vitreous or aqueous sample, as it is a really interesting and low invasive (if aqueous) way to validate a high clinical suspicion of VRL.
- The next section aims to determine which first-line treatment is mainly used (local treatment, systemic treatment or both) and how follow-up is performed by ophthalmologists, hematologists and neurologists. Also on the treatment used in case of intraocular involvement and which screening is performed to exclude secondary ocular involvement in case of pure PCNSL at diagnosis.
- Final section is related to gather participants' expectations from a future European taskforce on intraocular lymphoma.

The mapping exercise was launched in July 2020 and was disseminated through [dedicated pieces of news](#) for ERN-EuroBloodNet website and distributed through [ERN-EuroBloodNet monthly and dedicated Newsletter](#) and communication channels (Twitter, LinkedIn).

The exercise was opened until December 2020, allowing the gathering 86 responses from 20 countries. Answers are currently being assessed by the coordinators of the action in order to perform a deep analysis of the situation in Europe.

A preliminary analysis performed with first answers already shed some important results supporting the need for creating a European task force on the area and the expectations from its creation.

Further details on the survey content and first results can be found on Deliverable 4.4 ERN-EuroBloodNet Report on the availability of highly specialized procedures for rare hematological diseases, September 2020.



## TRANSCRANIAL DOPPLER FOR SICKLE CELL DISEASE PEDIATRIC PATIENTS

The mapping exercise was agreed among the expert team from the coordinators of the action including key questions on:

- Availability of TCD for SCD patients and standard protocol in the center and age range of patients
- Availability of TCD dedicated staff unit in the center
- Type of methodology used for TCD on SCD, follow up and number of TCDs performed
- Interpretation of the results and

The mapping exercise has been launched in February 2021 and is opened to date of the present deliverable.

Dissemination of the action is currently ongoing through [dedicated pieces of news](#), and through ERN-EuroBloodNet communication channels (Facebook, LinkedIn).



## 5. CURRENT STATE OF THE ERN-EUROBLOODNET INVENTORY OF MEMBERS AND EXPERTS

A total of 270 experts have already created their profiles in the ERN-EuroBloodNet directory, including both members representatives and substitutes and experts invited by them. 23 of them belonging to United Kingdom prior members have been hidden in order to be directly shown within the new Supporting Partners membership.

With the hidden of United Kingdom profiles and incomplete profiles (ie. selection of diseases of expertise is pending), a total of 174 experts profiles have fulfilled completely their profiles.

With the aim to integrate the relevant data introduced so far in the ERN-EuroBloodNet directory of members, the results reported in this deliverable are focused on the profiles completely fulfilled.

Comparing to previous year, a total of 15 new profiles have been created and/or completed. It is remarkable the increase of France with 5 new experts profiles on the area of lymphoid malignancies and Italy with 4 focussed on the non-oncological subnetworks.

Results of the number of experts by Member State dealing with oncological or non-oncological subnetworks are shown in table 1. In addition, the specific subnetworks by Member State are detailed in Figure 1.

MS	Experts	Non-Onc	Onc
BE	10	8	3
BG	1	1	0
CY	16	16	0
CZ	1	0	1
DE	3	0	3
ES	6	6	0
FR	35	23	12
IE	1	1	0
IT	67	48	23
LT	2	1	1
NL	17	17	2
PL	6	0	6
PT	5	4	1

Table 1. Number of experts dealing with non-oncological and oncological subnetworks by Country

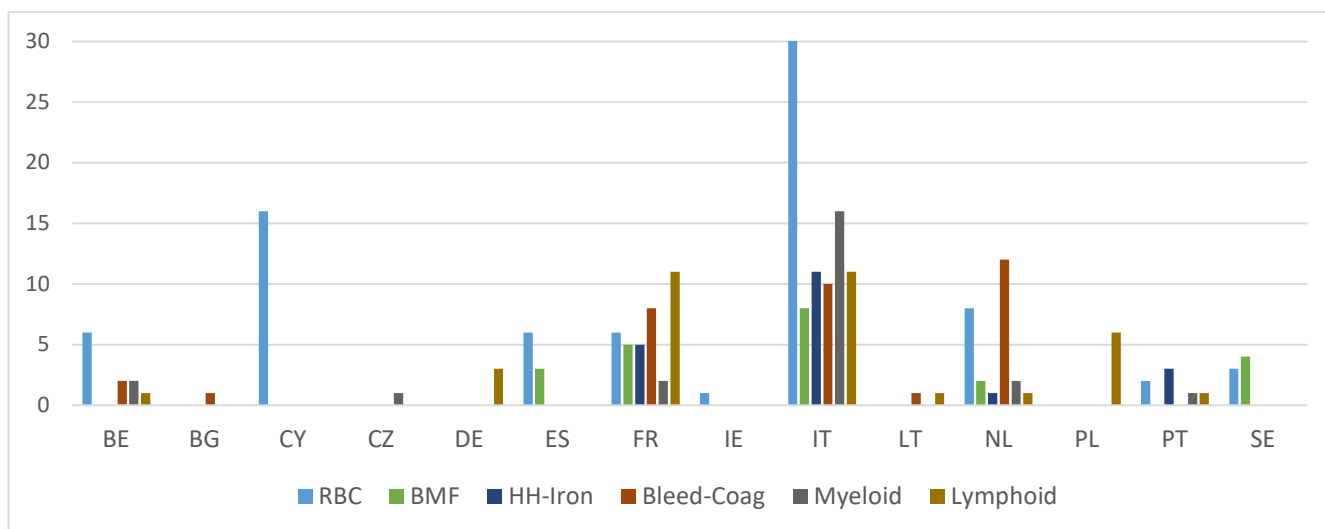


Fig 1. Number of experts by subnetwork and country. Subnetworks: Red blood cell disorders (RBC), bone marrow failures (BMF), Haemochromatosis and iron defects (HH-Iron), bleeding and coagulation (Bleed-Coag), Myeloid malignancies and lymphoid malignancies

In line with the results from previous years, Italy is the country with the highest number of experts in the ERN-EuroBloodNet inventory, which is normal taking into consideration that the number of Italian members is the highest in ERN-EuroBloodNet (21 from 66 members). Also their involvement in the Red Blood Cell disorders subnetwork, together with the high number of experts in Cyprus for this subnetwork, is logic since Thalassaemia is endemic in the Mediterranean area and the prevalence of this disorder belonging to the red blood cell subnetwork is very high comparing to non-endemic areas.

On the oncological area it is remarkable the increase of the experts profiles related to Lymphoid malignancies in France which has been almost duplicated in this period (from 6 to 11 experts profiles).

On the other hand, attending to the area of expertise of the experts fulfilling the profiles, some differences can be observed among the oncological and non oncological hub. Figure 2 shows the percentage of experts based on their expertise and hub.

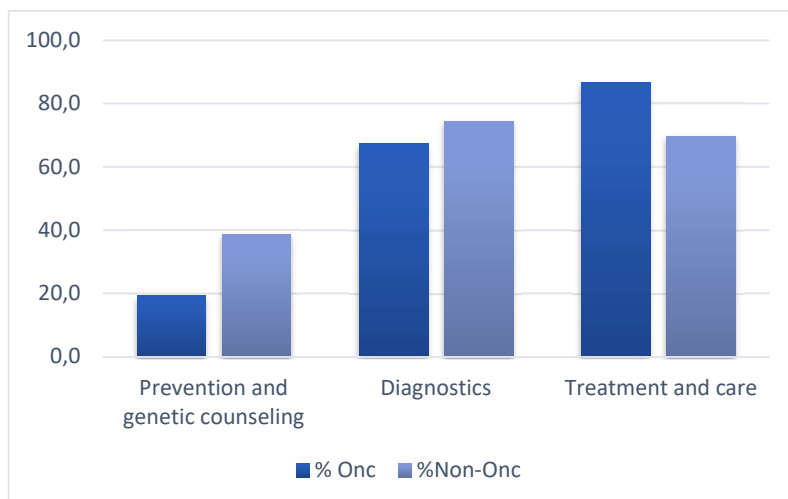


Fig 2 Percentage of experts by their area of expertise and dedicated hub

When focusing on the oncological diseases the trends has been maintained with regards to data from previous year in the area of treatment and care, being the vast majority (86,5%) of the health professionals involved. On the other hand, the percentage of diagnostics field has notably increased from to 60,9% to 67,3% of the experts devoted to this area and in the prevention and genetic area from 15,2% to 19,2%.

When analyzing the non-oncological hub, the general trends of the areas of expertise have been more stable than the oncological hub, with a slight decrease on the proportion of experts on the treatment and care (from 72,5% to 69,8%) and in prevention and genetic counseling area (from 40,4% to 38,8%). The marked preventive character of the non-oncological in comparison to the oncological diseases is manifested also in this period, where the percentage of experts on prevention represents the 40,4% of the profiles, while on the oncological hub the proportion is approximately half (19,2%).

Experts filling their profiles are also able to select their patients' age coverage. Figure 3 shows the percentage of experts dealing with children, adults or aged people by hub.

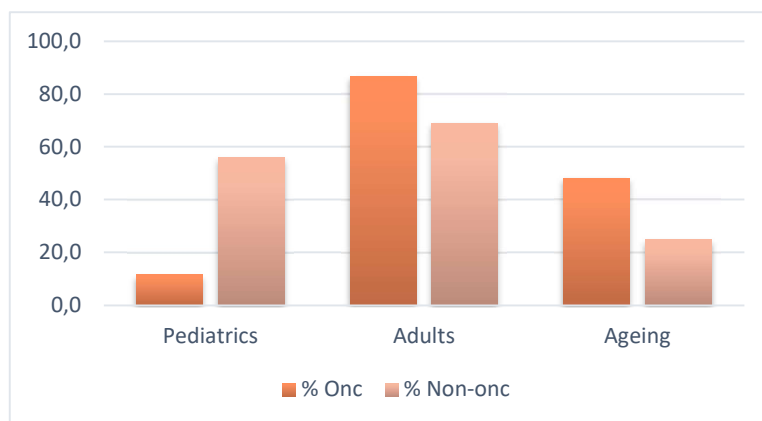


Fig 3 Percentage of experts by the patients' age dealing with and dedicated hub

The trends of this figure has been maintained with compared to previous year, highlighting a slight increase in the proportion of experts dealing with Ageing on the oncological hub (from 41,3% to 48,1% of the experts profiles).

Also, it is important to clarify that the low number of experts from the oncological hub dealing with pediatrics is given since these experts declared to deal with pediatrics, adults and ageing, however, oncological diseases in children are out of the scope of ERN-EuroBloodNet.

## 6. EXPECTED OUTCOMES & NEXT STEPS

ERN-EuroBloodNet mapping of healthcare services in Rare Hematological Diseases (RHDs) is cornerstone for setting the basis for a European model of networking. They rely on a validated identification of experts at both the national and European levels. It also arises the need for cross border health based on existing gaps in certain Member State for clinical management of a specific condition while allows health planning and better allocation of resources.

Making this expertise public through ERN-EuroBloodNet members' profile allows the establishment of new bridges for collaboration not only among experts but also with other European bodies such as EMA while enabling health professionals and patients seeking for best healthcare services across Europe. The EuroBloodNet mapping of healthcare services in RHD will also provide valuable information for identifying needs on best practices, continuing medical education and clinical and translational research.

Through this activity ERN-EuroBloodNet aims to build a central repository of reliable sources of information on expertise available at both national and European level in RHDs. To this aim, RHDs have been grouped into disease or disease groups (RHD-DGs) based on the analysis of codification schemes (ORPHA and ICD) for definition of rare diseases. The final version of the RHD-DGs has served as the basis for the upcoming tools and web redesign that has already been provided to the website developers.

Based on the results from this period of implementation, the following next steps are foreseen:

1. Finalize the implementation of experts profiles for the recent incorporation of Affiliated partners and future new members.
2. Creation of the new "Disease cards" website section where each RHD-DGs will have its own "card", showing all the interrelated actions/documents tagged in the website for the specific group. Each card will be composed by the following sheets:
  - a. Reference centers and experts: List of centers and experts which have selected the specific RHD-DGs of expertise will be shown
  - b. Patients associations - List of patients associations which have selected the sepecific RHD-DGs of coverage
  - c. Guidelines - List of Clinical Practice Guidelines and other Clinical Decision Making Tools tagged with the specific RHD-DG
  - d. Education - List of Past/Future webinars dedicated with the specific RHD-DG
  - e. Research - New section that will be implemented for the listing of observational studies and clinical trials where experts are involved
  - f. Ongoing projects - List of projects focussed on a dedicated RHD-DGs
3. Continue the analysis of the availability of HSP targeted for EU mapping, identified of high added value for the achievement of the evidence needed to facilitate the shaping of policies or even the establishment of cross-border pathways.



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