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

European Reference Networks

DELIVERABLE 1.1 ERN-EUROBLOODNET DEVELOPMENT STRATEGY

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

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Report document

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

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Short Description

Report (EN) describing main actions to ensure continuous smooth functioning, integration and expansion of ERN-EuroBloodNet members system

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1. INTRODUCTION

ERN-EuroBloodNet Development Strategy

The ERN-EuroBloodNet has been renewed in March 2022 for a period of 18 months after five years of implementation. This renewal is the occasion to learn from past experiences and to identify aspirations for the sustainability and the future development of the network. During the first five months of implementation, the coordinator, co-coordinator and scientific director, have prepared and detailed the ERN development strategy (D1.1 ERN-EuroBloodNet development strategy). This development strategy aims at guaranteeing the continuous and growing expertise of ERN members, while, providing the necessary support for their active involvement in the network's actions to tackle rare haematological diseases. This development strategy is based on five main pillars:

a) Integration of new members in the ERN and engagement in concrete actions

b) Procedure for expansion of disease coverage of ERN members

c) Provision of support in the evaluation process of ERN members, ie. Audits, monitoring exercises

d) Increasing of European Patients Groups Representation for Hematology

e) Work Plan for 18 months from March 2022 to August 2023

This ERN-EuroBloodNet development plan has been presented during the 3rd ERN-EuroBloodNet Progress Meeting, held on May 19th 2022. It has been sent afterwards to the Board of the Network (BoN) for final validation. Implementation of the strategy will be supported by the ERN Monitoring manager with the support of the Financial and Administrative manager.

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2. INTEGRATION OF NEW MEMBERS IN THE ERN AND ENGAGEMENT IN CONCRETE ACTIONS

At its launch in 2017, the ERN-EuroBloodNet consisted of 66 healthcare providers (HCPs) as Members. The UK withdrawal from the European Union took effect on 1 January 2021 and six UK HCPs ceased to be part of the network. However, ERN-EuroBloodNet continues collaboration with individual UK-based clinicians as Supporting Partners.

In 2019, the European Commission launched a new call for membership to the existing ERNs. Following this call, 38 new HCPs applied to join the ERN-EuroBloodNet. After going through a specific assessment process, the Board of Member States for ERNs (BoMS) announced the final decision and gave the result of the applications: A total of 36 new Members joined the ERN-EuroBloodNet on 1st January 2022, giving a total of 96 HCPs in 18 Member States (3 of these new Members were previously Affiliated Partners).

Through the inclusion of these new members, the ERN-EuroBloodNet has extended both Its disease and country coverage. As a result, ERN-EuroBloodNet has scaled-up the EU dimension of its actions. Although Italy remains the major represented country within the ERN, the country coverage has been extended to new European countries such as Denmark, Finland, Greece and Hungary (see figure 1).

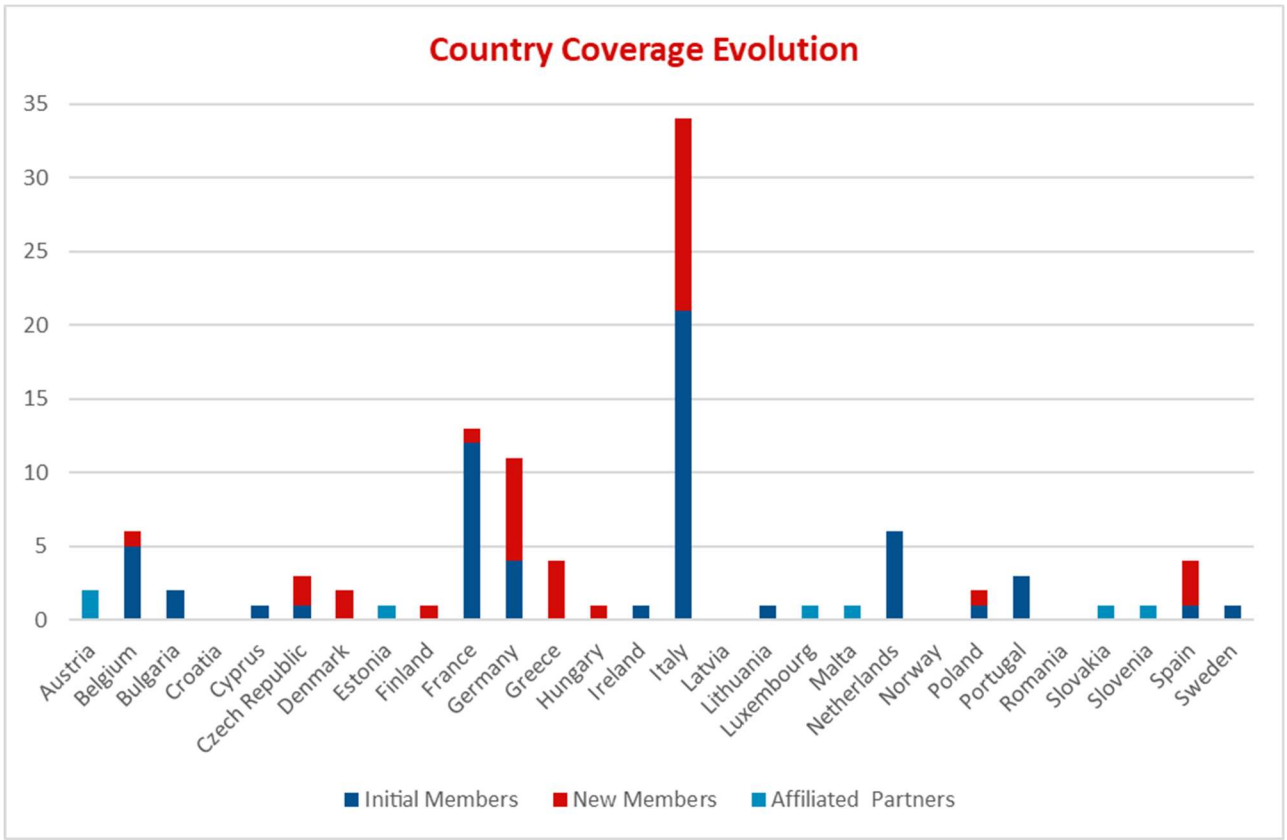

Fig. 1. *ERN-EuroBloodNet country coverage evolution with the Integration of New Members In the ERN In January 2022.*

The disease coverage has also been impacted by this integration of ERN new members: The majority of new members cover the oncological subnetwork, while the Red Blood cells defects and bleeding coagulation networks remain the most represented ones in the ERN (see figure 2).

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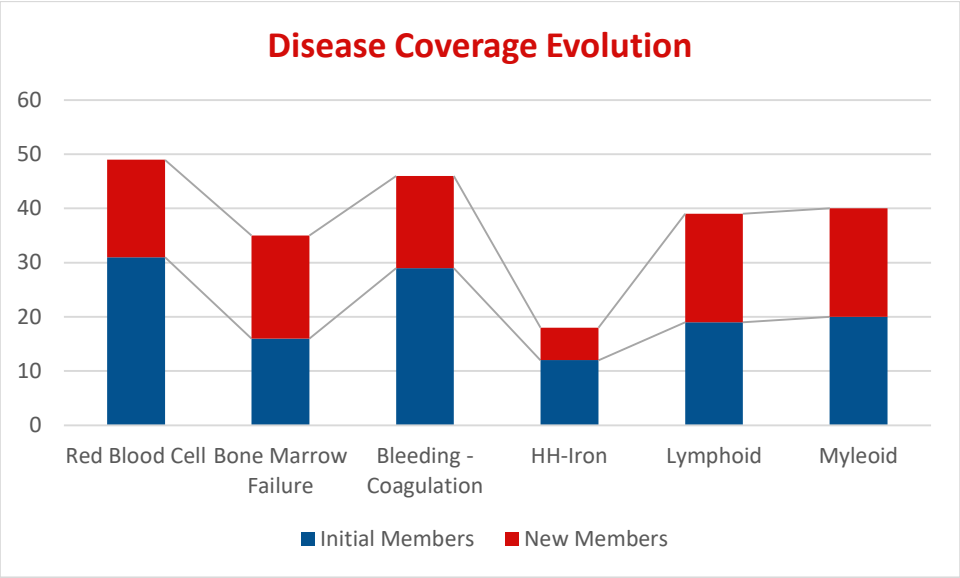

Fig. 2. *ERN-EuroBloodNet Disease coverage evolution with the Integration of New Members In the ERN In January 2022.*

OBJECTIVE

Ensuring a smooth and rapid integration of new ERN members represent one of the key objectives the network development strategy. The facilitation of this on-boarding process aims at involving rapidly and concretely new HCPs in the ERN system, to scale-up the ERN activities and share knowledge and expertise on rare haematological diseases at a wider level.

METHODS

The Networks wants to prioritize the engagement of new members through two different strategies: First, by assisting them in their on-boarding procedure, in collaboration with the European Commission.

Support is being provided for the different on-boarding phases that including the following steps:

1) Information to the applicants through the HCPA tool and by official letter from the network
2) On-boarding of new members:
   a) Data cleaning : Checking of administrative data and Integration to the mapping of experts of the ERN.
   b) Access credentials: New members have been invited to create their credential and request access to the CPMS.
   c) Provision of user training for the CPMS: A first virtual training has been provided by the EC on June 2022. Another CPMS workshop will be provided (online) in October 2022 by the ERN-EuroBloodNet to promote the use of the CPMS while assisting new members in the understanding of the platform.
   d) Distribution of the of logos : ERN logos will be prepared by the European Commission and shared with New members. After signing a bilateral sub-licensing agreement with the network, new ERN members will be able to use the logo in their communication and dissemination material.

To facilitate this on-boarding process, a welcome meeting gathered 108 participants has also been organized in March 2022 to explain to ERN-EuroBloodNet new members the above-mentioned steps of the on-boarding process. New centres keep assisted by the network in the process by mail.

The second pillar of this on-boarding strategy will be to promote the active involvement of new members in concrete actions developed by the ERN. These concrete actions have been presented and explained to the new members in various occasions, first of all in the Welcome meeting, but also in the ERN-EuroBloodNet 3rd Progress Meeting led on May 19th 2022. For this occasion, members were invited to express their needs through a collaborative table for launching new initiatives or integrate already existing ones within the ERNs. Outcomes from this meeting are being used to engage new members and integrate their needs and expertise to the current actions of the ERN. Finally, more targeted meetings will be organized based on Diseases subnetworks. These specific meetings will explain the ERN concrete actions in those areas of expertise of high interest for new members and show how they can actively contribute.

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RESULTS

ERN-EuroBloodNet New members are being assisted by the network in their on-boarding process, which is expected to be finalized in October 2022, after the reception of their ERN logo and their last CPMS training. The New Members Welcome Meeting and the 3rd ERN-EuroBloodNet Progress Meeting informed new members about the duties and opportunities Induced by their ERN membership. They enabled to identified key topics for the development of new and/or already existing actions:

- Long term strategy for accessing gene therapies
- Access to expensive drugs facilitation
- Development on tele-expertise
- Educational topics for webinars
- Patients involvement in Research and Clinical trials
- Contribution and building of European registries

The next ERN-EuroBloodNet Progress meeting (which takes place twice a year) will follow-up on these topics.

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3. EXPANSION OF DISEASE COVERAGE OF ERN MEMBERS

The disease coverage of the 24 ERNs was analyzed and discussed in 2015-2016 following a bottom-up approach in consultation with the broad rare diseases community, including Patient Associations, Scientific Societies, Member States and consultation bodies (Joint Action on Rare Diseases and Commission Expert Group on Rare Diseases).

Although the initial 24 Network proposals were quite exhaustive in terms of the diseases coverage, it has been deemed appropriate to consider in 2019, two years after the launch of the ERNs, whether any major gaps exist in the disease coverage of the Networks that need to be addressed. A comprehensive consultation with the ERNs was carried out, leading to an update of the disease coverage (including, when needed, new thresholds and criteria).

In this context, the European Commission has set up mechanisms for validating the extension of the disease coverage of ERNs and of their HCPs.

Currently, the ERN-EuroBloodNet's coverage involves a large group of hematological disorders resulting from quantitative or qualitative abnormalities of blood cells, lymphoid organs and coagulation factors. The coverage encompasses all Rare Hematological Diseases according to Orphanet classification, including rare hereditary hemochromatosis following a request from well-established patient groups and experts. These rare hematological disease are distributed into two thematic groups: oncological diseases and non-oncological diseases. Oncological diseases include two subthematic areas, and non-oncological diseases include four subthematic areas:

Non-Oncological Thematic Group
- Rare red blood cells defects
- Bone marrow failure and Hematopoietic disorders
- Rare bleading-coagulation disorders and related diseases
- Hemochromatosis and other rare genetic disorders of Iron metabolism and heme synthesis.

Oncological Thematic Group
- Lymphoid Malignancies
- Myeloid Malignancies

In order to guarantee the expertise of the members within the ERN-EuroBloodNet, specific criteria was defined for each of the 6 subnetworks, including a minimum number of patients for some specific disease groups and highly specialized criteria for the diagnosis and treatment of such disorders.

Due to this comprehensive coverage, the ERN-EuroBloodNet does not envisage any expansion of area of expertise at the moment. However, the possibility of actualizing the disease-coverage of ERNs members enables to assess the growing expertise of HCPs, while guaranteeing their continuous and increasing involvement Into the ERN's activities.

OBJECTIVE

To reach a comprehensive coverage of all rare hematological diseases by the ERN-EuroBloodNet, members will be encouraged to get their newly acquired expertise assessed and validated at the European level.

METHODS

In order to update their disease coverage, ERN members need to go through an application procedure required by the European Commission. The process, which is described in a "Protocol for managing disease areas within current ERN-Healthcare Providers"; includes the following steps:

Step 1: Members fill-in the template provided by the European Commission

Step 2: Members need to notify a copy of the application to the Member State's competent authority. Upon this notification, the Member State's competent authority may either: (i) endorse the application by issuing a letter of endorsement or similar certification at national level confirming that the existing member is recognised as an expert centre for this rare disease(s) or complex condition(s) in its Member State under their respective national legislation; or (ii) take note of the application without any further action within 30 days after the notification; or (iii) reject the application.

Step 3: The application will be peer-reviewed by the Board of the network of the ERN-EuroBloodNet, based on the already established specific criterias for each subnetwork of expertise.

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Step 4: The application will be assessed by the ERN Board of Member States (BoMS);

Step 5: After the decision of the BoMS, the EC will inform the applicants and the ERNs concerned about the decision.

Step 6: Follow-up of the extension of the disease coverage will be made mandatory and integrate the annual monitoring and 5-years evaluation of ERNs.

This application process in intented to take place annually, opening in January. Members need to be clearly Informed In advance about the procedure, and about criteria's of eligibility to be able to anticipate the call and apply In the best conditions as possible.

RESULTS

ERN-EuroBloodNet development strategy will include a strong focus on this disease-area expansion procedure in order to guarantee the adequate and actualized recognition of the members' expertise. As a result of the first call for extension of the disease coverage led in February 2022, a total of 4 ERN-EuroBloodNet members extended their expertise with the ERN. The assessment of their application has been officially communicated by the BoMS on April 2022.

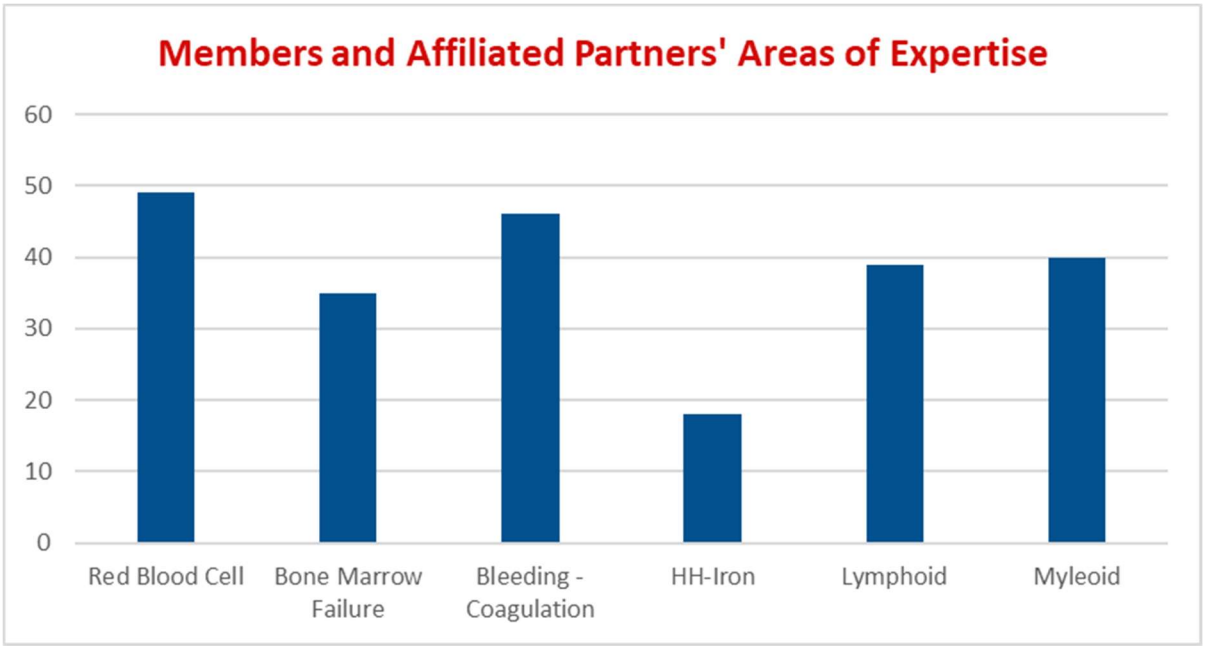

Fig. 3. *ERN-EuroBloodNet Disease Coverage after the extension of Expertise of 4 Member In 2022*

Information about the next call for disease-area expansion Is being provided during ERN-EuroBloodNet Progress Meeting. So far a total of 11 HCPs expressed their interest in extending their disease coverage In the next call that is expected to be open on January 2022.

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4. PROVISION OF SUPPORT IN THE EVALUATION PROCESS OF ERN MEMBERS

Given the central role of ERNs in treating, diagnosing and investigating complex and rare diseases, the quality of the care provided by its members is of high importance. Promoting and safeguarding a robust and feasible monitoring and evaluation system is therefore essential. Over the years, procedures have been developed to assess and monitor ERNs and their member, in particular through the AMEQUIS project (Assessment, Monitoring, Evaluation, and Quality Improvement System). In parallel, the Implementing Decision 2014/287/EU requires that an Evaluation Body appointed by the Commission should evaluate the Networks and their Members five years after their initial approval or last evaluation.

The general objective of this evaluation process is to verify and assess:
a) The fulfilment of the criteria and conditions set out in Delegated Decision 2014/286/EU
b) The accomplishment of the objectives set out in Article 12(2) of Directive 2011/24/EU
c) The outcomes and performance of the Network and the contribution of each Member
d) The achievement of the objectives and quality of the deliverables produced within the ERNs Specific Grant Agreements (SGAs)

This evaluation is expected to be launch in September 2022, and to last approximately one year. It will Include the following steps: (see figure 4).

Fig. 4: *Evaluation Timeline*

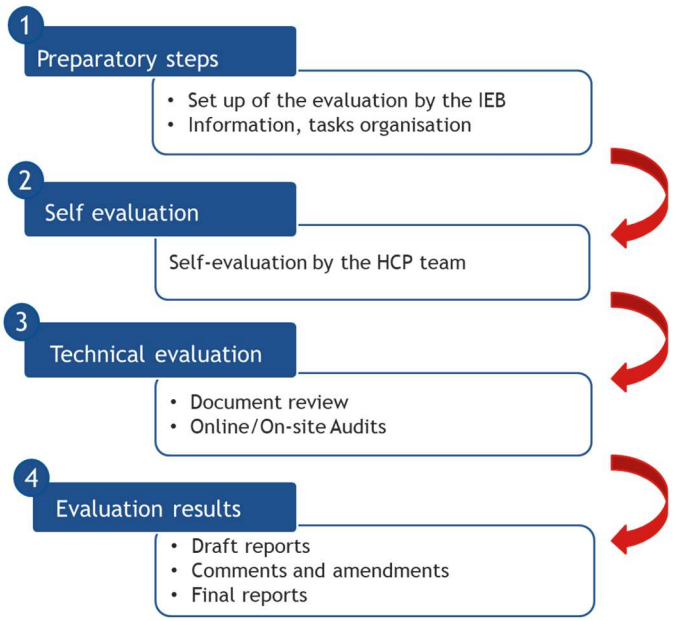

Fig. 5: *Steps of the Evaluation Process for HCPs*

Based on the results obtained in the evaluation of the Networks, the Independent Evaluation Body will provide a global evaluation report of the European Reference Networks system.
Outcomes from this process might be either:
- The continuation of the HCPs membership and/or of the ERN
- The implementation of an mmprovement plan of the HCP and/or of the ERN
- The termination of the HCP membership and/or of the ERN

OBJECTIVE

The network will provide support to ERN members in the process of the 5-years evaluation. This support aims at ensuring the realization of a qualitative evaluation so the Independent assessment body can clearly Identify benefits and challenges In the ERN

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system. Results from this evaluation will be analyzed for the development strategy of the ERN-EuroBloodNet. This support to HCPs also aims at guaranteeing the best evaluation outcomes as possible, resulting in the continuation of HCPs membership.

METHODS

Several pillars have been identified for the development of this supporting strategy to HCPs:

- Ensure adequate and complete information: The network will guarantee the accurate and complete Information of all ERN-EuroBloodNet members regarding the evaluation process. The Evaluation Manual and Tool box, provided by the European Commission will be shared in advanced. Information on the process and on these manuals will be provided during the bi-annual Progress Meetings of the network and during specific and dedicated meetings on the process.
- Facilitation of the Evaluation process: The network will provide simplified tools and documents to its members for facilitating the preparation of the Evaluation. In particular, a document presenting a general overview of the key Information for HCP will be shared, Including:
    - Timelines for the Evaluation
    - Steps of the evaluation
    - Key Measurable elements for HCPs
    - Scoring guidelines
    - Evidence required
- Identify issues and potential breaks: The Network will gather every issue or challenge identified by its members and alert the European Commission and the Independent Evaluation body In advance to prevent any obstacle or difficulty for the Evaluation process.
- Sharing of good practices and harmonization among ERNs: A meeting will be organized with other ERNs project managers in order to share experience and good practices on this evaluation process. This meeting will also enable to harmonize practices for supporting HCPs In the evaluation process, especially for those centres, which are part of several ERNs.

RESULTS

ERN-EuroBloodNet members have received the Evaluation Manual Tool box and the general information regarding the Evaluation process and timeline. Two first informative meetings on the HCPs Evaluation have been held on July 7th and July 21st 2022 (online). Based on these meetings, some questions and challenges have already been identified to be presented to the European Commission and the Independent evaluation Body. As a result of this support action, the network will ensure a smooth process of the HCPs Evaluation and therefor, optimize the results obtained after this evaluation.

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5. INCREASING OF EUROPEAN PATIENTS GROUPS REPRESENTATION FOR HEMATOLOGY

In parallel to the establishment of European Reference Networks (ERNs), EURORDIS - Rare Diseases Europe has initiated the creation of European Patient Advocacy Group (ePAG) for each ERN to bring together the patient organisations whose rare diseases are covered by a specific ERN such as ERN-EuroBloodNet. The ePAG Advocates are nominated to represent their disease area in the ERN-EuroBloodNet as well as the interests of the wider patient community affected by rare hematological diseases.

ePAGs constitute one of the main cornerstones of the European Reference Networks. The involvement of patients' organizations in the Board of the ERN- EuroBloodNet has been assured from the beginning in order to guarantee their pivotal role within the network and keep the ERN-EuroBloodNet patients' centred approach. Their role could be invested in several domains:

- Ensuring patient-centred care and respect for patients' rights and choices
- Ensure transparency in quality of care, safety standards, clinical outcomes and treatment options
- Ensure that ethical aspects for patients are properly taken into account in balancing patient and clinical needs
- Contribute to the development of information for patients on health policies, good clinical practice, treatment pathways and dissemination of guidelines
- Contributing to the planning, monitoring and evaluation of ERN initiatives
- ERN-EuroBloodNet Cross Border Health assistance to Rare Hematological Diseases patients, an infopoint for patients dealing with Cross Border Health Rights.

OBJECTIVE

The main objective fixed by the Network has been to increase the European patients' groups' representation for Hematology according to pre-identified gaps in the representation of not covered clinical areas

METHODS

The nomination of ePAGs is regulated according to EURORDIS internal rules. It is the fundamental, strategical and joint collaboration among ERN-EuroBloodNet coordination team and EURORDIS. The action consisted of two mains steps: identifying those clinical areas not yet covered by a European patient representative and secondarily together with EURORDIS identifying potential candidates.

RESULTS

Increase of ePAGs for Hematology:

• Several gaps have been identified regarding patients' representation in the network, as the areas of Sickle cell disease (SCD) and Pyruvate Kinase Deficiency (PKD). Finally, considering the large number of diseases included in the lymphoid subnetwork and myeloid subnetwor, it has been chosen to having other ePAGs supporting the ERN.

- Natacha Bolaños from Lymphoma Coalition has been named ePAGs for Lymphoid Subnetwork.
- Jacqueline Dubow from MDS Alliance and Connaître et Combattre les Myélodysplasies (CCM)has been named ePAGs for Myeloid Subnetwork.
- The cooperation with a patient representative from PKD Contactgroup has been strengthen and proposed to be formally recognized as ERN-EuroBloodNet ePAG.
- For SCD, more efforts need to be done for identifying an adequate candidate. Description of the ongoing procedure is developed in the paragraph 2.3 of this Deliverable.

The ERN-EuroBloodNet is represented by 10 ePAGs affiliated to 12 different International or European Patients Networks and to EURORDIS too, as it covers all Rare diseases, finally 6 ePAGs contribute also to National Support Groups, as listed:

1. Jan Geissler from CML Advocates Network (International) and Leukemia Patient Advocates Foundation (European)
2. Loris Brunetta from Thalassaemia International Federation (International) and Associazione Ligure Thalassemici Onlus (National)
3. Sophie Wintrich from MDS UK Patient Support Group (National) and MDS Alliance (European)
4. Baiba Ziemele from Latvia Hemophilia Society (National), European Haemophilia Consortium (European) and Latvian Alliance of Rare Diseases (European)

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5. Ananda Plate from Myeloma Patients Europe (European)
6. Maria Piggin from PNH support Group (National) and PNH Global Alliance (International)
7. Pierre Aumont from Ensemble Leucémie Lymphomes Espoir (National) and Chronic Lymphocytic Leukemia Advocates Network (European)
8. Dag Erling Stakvik from European Federation of Associations of Patients with Haemochromatosis (European)
9. Natacha Bolaños from Lymphoma Coalition (International)
10. Jacqueline Dubow from MDS Alliance (European) and Connaître et Combattre les Myélodysplasies (National)

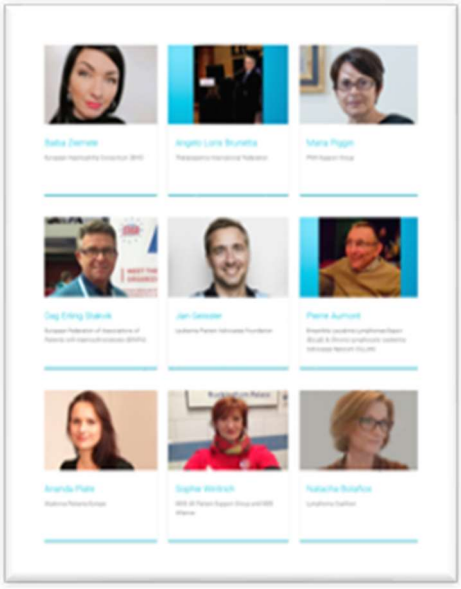

Fig 6. *In the figure are listed the Pan-European Network of Hematology Patients Organisations of the 9 ePAGs affiliated to the ERN-EuroBloodNet. All ePAGs are affiliated also to EURORDIS, some of them contributes also to National Support Groups. Picture of the 10th ePAGs, Jacqueline Dubow will soon be added.*

As next steps, the designation of an EPAG for PKD and for SCD will be finalized.

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6. WORK PLAN FOR 18 MONTHS FROM MARCH 2022 TO AUGUST 2023

The ERN-EuroBloodNet has been recently renewed for a period of 18 months. This new "bridging grant" has been accepted retro-actively and will last from march 2022 to august 2023. ERN-EuroBloodNet's general aim for the next stage is to ensure the continuation of the coordination, management and operational activities of the network enabling RHD patients and health professionals to benefit from pooling of expertise, knowledge and resources at the European level and to receive the appropriate diagnosis and treatment as well as enhance knowledge generation, training and research in the area of RHDs.

The Grant agreement signature for this Bridging Grant is expected to be performed by summer 2022, and the grant's pre-financing to be received by autumn 2022. Given the very short deadline for the Implementation of an ambitious programme, activities and work plan for the duration of the project need to be clearly organized and distributed to avoid any delay and maximize the networks' results and Impact.

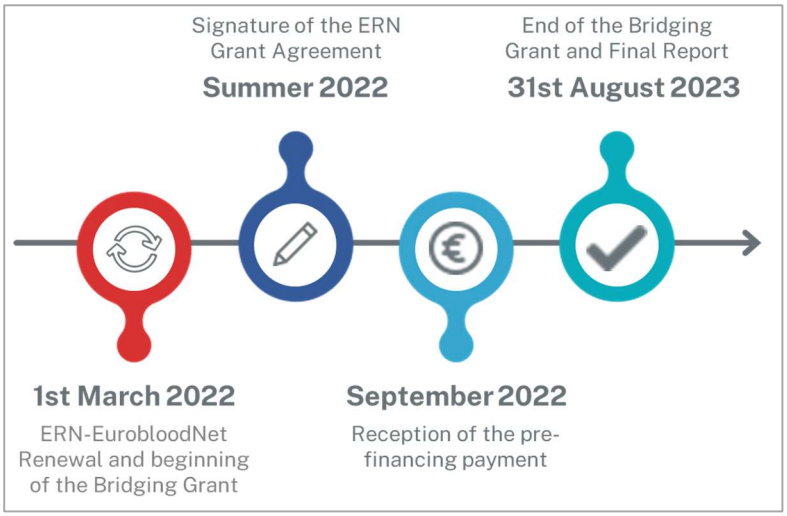

Fig.7: *General Bridging Grant Timeline*

OBJECTIVE

Define and develop a clear work plan for the ERN-EuroBloodNet bridging grant to maximize the Impact and results of the project.

METHOD

Methods and tasks aiming to achieve ERN-EuroBloodNet objectives for the upcoming period of implementation have been split into the following 6 Working Packages (WP):

- **WP1:** Coordination
- **WP2:** Dissemination
- **WP3:** Evaluation
- **WP4:** CPMS Activities
- **WP5:** Other digital activities of ERNs
- **WP6:** Training and education

A specific meeting has been organized within the ERN-EuroBloodNet coordination team to plan the work to be done in the following months and to establish a clear workplan to follow. This meeting, held on July 2022, enabled to identify potential breaks or challenges in the activities planned.

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RESULTS

Deliverables Gantt Chart has been revised according to new timelines and challenges identified (see figure 8).

DELIVERABLES	ERN-EuroBloodNet - Revised Deliverables Gantt Chart																	
	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M13	M14	M15	M16	M17	M18
	mar-22	apr-22	may-22	jun-22	jul-22	aug-22	sep-22	oct-22	nov-22	dec-22	jan-23	feb-23	mar-23	apr-23	may-23	jun-23	jul-23	aug-23
D1.1 Development strategy																		
D2.1 ERN-EuroBloodNet Dissemination plan																		
D3.1 ERN-EuroBloodNet evaluation plan																		
D5.1 ERN-EuroBloodNet report on monitoring exercises																		
D2.2 ERN-EuroBloodNet Dissemination report																		
D3.2 ERN-EuroBloodNet evaluation report																		
D4.1 ERN-EuroBloodNet report on CPMS																		
D5.2 ENROL statistical analysis																		
D6.1 ERN-EuroBloodNet report on educational actions																		
D6.2 ERN-EuroBloodNet report on CPGs and other CDMTs																		

Fig.8: *Revised Deliverables Gantt Chart*

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European Reference Network
for rare or low prevalence complex diseases
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