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

Periodic / Final Technical Report

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Acronym:
ERN-EuroBloodNet

Title:
European Reference Network on Rare Hematological Diseases

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ACKNOWLEDGEMENTS

We would like to thank all persons and institutions that have contributed to making ERN-EuroBloodNet a useful and realistic network during its second year of implementation with the final aim to improve how rare haematological diseases are tackled across Europe:

1. The European Commission, by means of its Consumers, Health, Agriculture and Food Executive Agency (CHAFEA);

2. The Scientific and Strategic Board members and their institutions that have actively contributed to the scientific implementation of the network;

3. All the ERN-EuroBloodNet members and experts who have collaborated in the different activities performed across Europe;

4. The European Patient Advocacy Group on hematology (ePAG) deeply committed with the activities performed by the network in representation of the patients affected by rare haematological conditions

1. DESCRIPTION OF THE ACTIVITIES CARRIED OUT BY THE BENEFICIARIES AND OVERVIEW OF THE PROGRESS

1.1. Description of the activities carried out during the reporting period in line with Annex 1 to the Grant Agreement

- Main activities carried out including methods and means

According to Orphanet classification, Rare Hematological Diseases (RHD) covered in ERN-EuroBloodNet involve more than 450 different diseases with differential clinical and etiological features avoiding the implementation of a unique methodological approach for reaching the common goals of the network, ie oncological vs non-oncological, hereditary vs acquired, or significant difference prevalence, among others. However, in despite of this fact, some unmet needs are common to all RHD as proved during the 1st year of implementation of the network:

a) There is no accessible repository of human and technical resources available to challenge the difficulties of RHD at the EU or national levels leading to an increase in the time of diagnosis and the number of patients misdiagnosed, as well as a lack of decision-making support.

b) There is no public comprehensive repository of reliable guidelines. Compounded by the fact that curricula for hematology differs widely across Europe and little time is dedicated to the rarest RHD, the delivery of highly specialised quality care is difficult to achieve.

c) Management of complex cases may require inter-professional consultation with of experts from a multidisciplinary team who may not be physically in the same institution or MS.

d) Finally, the scarce number of patients suffering from a RHD and the unawareness of their location frequently prevent the activation of clinical trials or collaborative research projects.

Accordingly, activities developed in the first year of implementation of ERN-EuroBloodNet were focussed to map the existing expertise and facilities available for RHD in the network as starting point for objectives deployment in the consecutive phases. Based on the results, the annual programme for the second year was structured in the following tasks and actions. **Full description of each task and subtask are included in the section 1.7 Description of the activities carried per WP**.

WP 3 – TFA 1 – CROSS BORDER HEALTH

ERN-EuroBloodNet Specific Objective 1 linked to TFA1: Improve equal access to highly specialised healthcare delivery for RHD across Europe.

Task 1.1 Mapping of services (clinical and diagnosis) available in Europe for best clinical care

1.1.1 Updates on the ERN-EuroBloodNet inventory of experts and members

The updates on the ERN-EuroBloodNet inventory of members and experts encompassed a) the revision of ORPHA classification for Hemochromatosis and other

rare genetic disorders of iron metabolism and heme synthesis subnetwork for the inclusion of porphyrias and ferrinopathies, b) improvement of the interface for the selection of diseases from the ORPHA classification in the departments and experts profiles and c) implementation of the disease search tool

1.1.2 State of the art of Bone marrow transplantation and Next generation sequencing for non-oncological rare haematological diseases

Two online surveys were conducted for the analysis of the state of the art of bone marrow transplantation (BMT) and next generation sequencing (NGS), as highly specialized procedures presenting high inequalities across EU in the context of non-oncological RHD.

Task 1.2. Establishment of a model for cross border referral system - Directive 2011/24/EU

An agreement for cross border health on BMT for Sickle Cell Disease (SCD) has been launched among two ERN-EuroBloodNet members, from Italy and Ireland. A task force and plan has been defined for the analysis of most conflictive issues faced for the establishment of the agreement and its translation into a practical toolbox aiming to facilitate the establishment of future cross border collaborations.

WP 4 – TFA 2 – BEST PRACTICES

ERN-EuroBloodNet Specific Objective 2 linked to TFA2: Promote best practice in prevention, diagnosis and clinical care across EU

Task 2.1. Create a comprehensive public database of reliable guidelines

2.1.1 Expansion of the List of international guidelines and recommendations

The first list of international guidelines and recommendations produced in the previous period of implementation was reviewed and expanded in order to produce a second version as extensive and comprehensive as possible.

2.1.2 Classification of guidelines and recommendations based on Quality domains

The guidelines and recommendations compiled were classified on three quality domains: a) Scope and purpose, b) patients' involvement and c) rigour of development.

Task 2.2. Assessment of the level of awareness and implementation of existing guidelines

2.2.1 Diseases and indicators identified for assessment of the holistic clinical management of RHD conditions including prevention, diagnostic tests, treatment and follow up.

The first key indicators for the assessment of guidelines and recommendations awareness and implementation have been identified focused on a) Concrete guidelines/recommendations addressing specific disorders which are expected to be poorly implemented and b) Clinical outcome indicators having some pointing to the minimal requirements (standard of care) and/or related to highly specialized procedures.

2.2.2 Assessment of the implementation of the Consensus recommendations on the diagnosis of pyruvate kinase deficiency (PKD)

IN the field of diagnosis, assessment of implementation was initiated for the PKD recommendations "Addressing the diagnostic gaps in pyruvate kinase deficiency: Consensus recommendations on the diagnosis of pyruvate kinase deficiency" based on a European mapping of centers performing PKD diagnosis and facilities for accurate diagnosis and genetic characterization. In addition, the establishment of the

External Quality Assessment on PK diagnosis has been launched in collaboration with UKNEQAS

WP 5 – TFA 3 – CONTINUING MEDICAL EDUCATION

ERN-EuroBloodNet Specific Objective 3 linked to TFA3: Disseminate cutting-edge knowledge and facilitate continuing medical education in the field of RHDs

Task 3.1. Identification of educational GAPs survey in collaboration with EHA

3.1.1 ERN-EuroBloodNet questionnaire on Continuing Medical Education

A questionnaire was conducted among ERN-EuroBloodNet members in order to a) compile educational material for professionals or patients and b) identify and assess the educational needs within the network.

3.1.2 Repository of Sickle Cell Disease Therapeutic Patient Educational material

A complementary questionnaire on the available educational material for SCD patients has been defined since the level of awareness of the disease and the presence of the patients organizations at the national level are extremely varied across MS. The objectives are to a) expand the educational material available compiled via the questionnaire on continuing medical education b) collect patients' opinion about the therapeutic patient educational domains to be covered.

New Task 3.2 Webinars program for health professionals

ERN-EuroBloodNet has defined a Webinar program to contribute to continuing medical development requirements of health professionals focussing on a very innovative and specific disease, clinic or intervention area.

Task 3.3. Co-organization with the ePAGs of European symposia with interactive patient participation

ERN-EuroBloodnet, ePAGs and the Hematology ePAG Project Management Office have co-organized the “EHA Capacity Building Meeting” within the 23rd EHA congress.

Task 3.4. Identification of areas including highly specialized procedures requiring short stays for the acquisition of expertise.

Three highly specialized centers as well as concrete agendas, teachers and topics have been defined for the organization of short stays on Paroxysmal nocturnal hemoglobinuria (PNH) Aplastic Anemia (AA).

WP 6 – TFA 4 – Telemedicine

ERN-EuroBloodNet Specific Objective 4 linked to TFA4: Provide inter-professional consultation by sharing of expertise and safe exchange of clinical information

Task 4.1. Pilot testing of the CPMS

The CPMS was open to ERNs by November 2017, starting a pilot phase until March 2018. ERN-EuroBloodNet participated in the pilot phase, including a report sent to the EC gathering the feedback from first users.

New Task 4.2 ERN-EuroBloodNet strategy for promoting the wide implementation of the CPMS

In order to ensure an efficient and effective implementation of the CPMS, an ERN-EuroBloodNet strategy for the promotion of the use of CPMS was defined including:

4.2.1 CPMS promotion and awareness among members

Broader dissemination of CPMS awareness among ERN-EuroBloodNet members either by online means or face to face meetings.

4.2.2 Upgrade of RHD categories in the "Preferences" section

ERN-EuroBloodNet identified the upgrade of the RHD classification available in the "Preferences" section as the first action to be performed for ensuring its efficient use. A new proposal for the disease categories to be included in the "Preferences" section has been discussed with CPMS IT Central for its implementation in the platform.

WP 7 – TFA 5 – Clinical Trials and Research

ERN-EuroBloodNet Specific Objective 5 linked to TFA5: Foster European cooperation in highly specialised procedures for diagnosis, innovative treatments and research

Task 5.1. To facilitate European epidemiological surveillance of RHD by promoting the creation of a European registry of patients affected by a RHD

A first analysis of the different strategies to be implemented for the establishment of a central European registry covering all RHD has been undertaken based on the different prevalence of the diseases tackled by the network. In addition ERN-EuroBloodNet has promoted the participation of expert centres and national registries in the Rare Anaemia Disorders European Epidemiological Platform (RADeep) while ensuring the application of recommendations released by the EU-RD-platform.

Task 5.2 To promote the participation in clinical trials

Two main actions have been undertaken for the promotion of participation of Clinical trials (CTs):

5.2.1 Analysis of the state of the art of on-going CTs for rare hereditary anaemias

In order to establish the state of the art of on-going clinical trials for rare hereditary anaemias (RHAs) a desk research was conducted on ClinicalTrials.gov website.

5.2.2 ERN-EuroBloodNet sponsoring CTs

Based on the results from the analysis of the state of the art on CTs, ERN-EuroBloodNet has therefore started to conduct academic CTs in very rare diseases.

- Coordination with other projects or activities at European, National and International level

WP2 - DISSEMINATION

Task 5 – Relations with third parties

5.1 Promotion of collaboration agreements with third parties

In order to create a real network it is essential to create synergies with other ERNs, projects and initiatives working towards objectives complementary to those of ERN-EuroBloodNet. Links for collaborative agreements have been already established and consolidated during this second year, eg. Orphanet, EURORDIS, patients' associations and National and International Scientific organisations. **Activities undertaken specifically with each third party are included in section 1.7 Description of the activities carried per WP.**

a) Transversal activities to all ERNs

European Commission and ERNs Coordinators Group

After the official approval for the 24 ERNs, a supra level group of coordinators was created for facilitating the gathering of different needs on common issues across the ERNs, sharing different points of view and facilitate the bidirectional communication with the EC.

The ERNs coordinators groups (ERNs CG) is formed by the 24 coordinators of ERNs, and during the second year it works under the coordination of Prof Franz Schaefer (ERKNET).

Cross-ERN Task Force meeting on eHistopathology

Histopathology expertise across Europe in the diagnosis of rare diseases is an eminent task across all ERN and can be accomplished by developing a common, web-based digital pathology network. In this context a new Cross-ERN task force was created to tackle this area.

European Commission – Joint Research Center (JRC)

The Joint Research Centre (JRC) is the European Commission's science and knowledge service which employs scientists to carry out research in order to provide independent scientific advice and support to EU policy.

The JRC in collaboration with DG SANTE are developing the European RD registry infrastructure (ERDRI) aiming 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.

European Joint Programme (EJP)

The European Joint Programme (EJP) on Rare Diseases brings over 130 institutions from 35 countries to create a comprehensive, sustainable ecosystem allowing a virtuous circle between research, care and medical innovation. EJP has been established to further help in coordinating the research efforts of European, Associated and non-European countries in the field of rare diseases and implement the objectives of the International Rare Disease Research Consortium (IRDiRC).

b) Rare Hematological Diseases

ORPHANET

Orphanet is the reference portal for information on rare diseases and orphan drugs, for all audiences aiming to help the improvement of the diagnosis, care and treatment of patients with rare diseases.

European Hematology Association (EHA)

EHA is a non-governmental and not-for-profit membership organization that is guided by its mission to promote excellence in patient care, research and education in hematology.

European School of Hematology (ESH)

The European School of Haematology (ESH) is a not-for-profit institution for continuing education founded in 1985 to promote and facilitate access to state-of-the-art and cutting-edge knowledge in haematology and related disciplines at the European level. ESH Conferences present state-of-the-art science and insight into new developments in the fields of basic, clinical and therapeutic research in Haematology.

European Joint Action on Rare Cancers (JARC)

The public health challenge posed by rare cancers combines both the typical problems of rare diseases (such as the limited professional expertise available in the community, or the difficulties in clinical research) and those of cancer, with the need of a timely and appropriate diagnosis and optimal treatment from the very beginning of the patient's journey. The Joint Action on Rare Cancers (JARC) is aimed to integrate and maximize efforts of the European Union (EU) Commission, EU Member States and all stakeholders to advance quality of care and research on rare cancers.

c) Patients

EURORDIS

EURORDIS represents more than 270 rare disease organisations from 32 countries, 19 of which are EU member states, and thereby reflects the voice of an estimated 30 million patients affected by rare diseases in the EU. One of its most important activities was the promotion of national centres of expertise and European Reference Networks.

Patient's Associations

Patients are one of the main motor of the ERN-EuroBloodNet. The network seeks direct contact with those organizations supporting patients living with RHDs and their families.

- Sponsorship

There are no other external sources of contribution to the activities reported in the project.

- Project Coordination (WP 1)

WP1 - COORDINATION AND EVALUATION

The general objective of ERN-EuroBloodNet Coordination was to establish a management programme for the efficient overall coordination of the network necessary for fulfilling ERN-EuroBloodNet's outcomes and specific objectives.

Specific objectives:

- To facilitate interaction with EU Commission officers.
- To ensure the effectiveness of network's management and monitor on-going activities
- To complete the project deliverables within the required time and under the established standards of quality.
- To ensure the communication flow between partners and promote co-operation in between sub-thematic areas and transversal fields of action, as well as to facilitate group-discussion to solve problems that may come up.
- To organize ERN-EuroBloodNet meetings, agenda, schedule and report on outcomes and agreements reached.
- To solve any problems that may come up during the network's completion both technical and financial

Coordination methodology

ERN-EuroBloodNet coordination methodology refers to all aspects concerning the tasks management, quality assessment and evaluation of their interactivity, progress and final results. The coordination methodology should ensure full involvement of all participating partners in the programmed tasks, in the collection of data and in the continuous feedback of ideas and needs. This is strictly necessary to guarantee

compliance with the multiannual work plan and the achievement of ERN-EuroBloodNet objectives and outcomes.

Management structure

Management of a network like ERN-EuroBloodNet, that includes 66 HCPs from 15 different Member States, and in spite of the fact that many of them have worked together in previous networks, requires strict organization in order to allow smooth running of the ERN.

EURORDIS has designed for ERN-EuroBloodNet 7 ePAGs that are structurally part of the development of the whole network. ePAGs role have been ensured in the coordination of transversal fields of action and subnetworks and are part of the Board of Network and of the Scientific and Strategic Board, ensuring a solid patients' centered approach.

Vertical coordination: Hubs of coordination and subnetworks

ERN-EuroBloodNet is based in two main hubs of coordination: 1) the oncological hub, based in Paris (AP-HP, Hôpital St. Louis), coordinated by Prof. Pierre Fenaux and 2) the non-oncological hub, based in Belgium (Hôpital ERASME-CUB, LHUB-ULB), coordinated by Prof. Béatrice Gulbis.

Following this structure, ERN-EuroBloodNet ensures the coverage of RHD through their inclusion in two main hubs: the oncological diseases hub (including two subnetworks) and the non-oncological diseases hub (including four subnetworks).

In order to ensure the involvement of patients' representatives in all the activities undertaken by the network, it was agreed to define 3 coordinators for each subnetwork, including two health professionals and one ePAG's representative.

Subnetworks coordinators defined for the 1st year of implementation have been maintained during the 2nd year of ERN-EuroBloodNet and can be found at: https://www.eurobloodnet.eu/subnetworks

Roles of the six sub-thematic areas chairpersons have been to:

- Ensure the smooth functioning of the subnetworks and their adequacy to the outcomes to be achieved
- Identify problems and take corrective measures when needed
- Inform the head of the TFA if deviations of the multiannual working plan are observed

Transversal coordination:

a) Transversal Field of Actions (TFAs)

Transversally, methods and tasks aiming to achieve ERN-EuroBloodNet specific objectives have been split into five categories of Transversal Field of action (TFA): 1) Cross border health, 2) Best practices, 3) Continuous medical education, 4) Telemedicine and 5) Clinical trials and research.

Each TFA is coordinated by one representative from the oncological hub, one representative from the non-oncological hub and one ePAG's representative in order to ensure a balance and equal contribution of different perspectives.

TFAs coordinators defined during the 1st year of the network have been maintained during 2nd year of ERN-EuroBloodNet implementation and can be found at: https://www.eurobloodnet.eu/transversalfieldsofaction

The roles of the TFA coordinators have been to:

- Ensure that objectives are achieved by all the subnetworks at the same level
- Take correcting measures when deviations are observed
- Address the main problems that may occur and communicate them to:

- Subthematic area chairpersons where the problem has been found in order to find a solution
- The hub coordinator if solution is not found

b) Concrete projects

During ERN-EuroBloodNet second year of implementation a new strategical structure was defined in order to promote the direct participation of members on the different ongoing actions launched by the network while facilitating their coordination and monitoring (see 1.3. Project Results and Visibility – Major problems and lessons learned).

In this context, a first list of 15 concrete projects was launched focused on the different Transversal Fields of Action and RHD areas where members are actively involved. This list is in continuous evolution and expansion since all members are welcomed to suggest and launch new concrete projects under the umbrella of the network.

Functional structure

ERN-EuroBloodNet has a clear governance and coordination structure that includes mechanisms to support oversight and evaluation, composed by:

Coordination team

Based on previous networking experience on pilot European networks, high skilled specialized profiles of the coordination team members are cornerstone for the success of effective networking implementation. ERN-EuroBloodNet's coordination team has been in charge of assuring the proper operational management of the network ensuring the smooth functioning among the key players involved, and thus, their involvement is needed from the outset and until the finalization of the action.

The coordination team is formed by:

Coordinator: Prof P. Fenaux, based in France, Hôpital St. Louis, head of ERN-EuroBloodNet and head of the oncological hub for this period is in charge of supervising all the activities performed in the network as well as be the responsible for the technical and financial management as well as time adherence to the schedule. He is also in charge of designing the MWP.

Co-coordinator: Prof B.Gulbis, based in Belgium, Hôpital ERASME, Head of the non-oncological hub for this period. She is involved in the main aspects of the operational management as second head of the network. She assumes the responsibilities of the coordinator when needed.

Scientific director, Dr M Mañú Pereira and IT and dissemination manager, Victoria Gutierrez Valle, both based in Barcelona, Spain, moved from Josep Carreras Leukaemia Research Institute to University Hospital Vall d'Hebron – Vall d'Hebron Research Institute being effective for the 2nd year of FPA implementation and regulated through collaboration agreement between AP-HP and University Hospital Vall d'Hebron – Vall d'Hebron Research Institute.

Scientific director: Dr M. Mañú Pereira, based in Spain, University Hospital Vall d'Hebron – Vall d'Hebron Research Institute, she directly assists the ERN coordinator in drafting the MWP, co-chair the Board and Committees meetings, and coordinates TFAs activities in line with ERNs coordinators group.

IT and Dissemination manager: V. Gutierrez Valle, MSc, based in Spain, University Hospital Vall d'Hebron – Vall d'Hebron Research Institute, contributes to implement the dissemination plan, website design including on-line applications and system for patients' voices, promote CPMS, prepare minutes of network minutes.

ERN and coordinator assistant: M. Pellegrini, based in Paris, Hôpital St. Louis, is in charge of organizational issues related to coordinator agenda, Board and Committee

meetings (venue, catering, travels and accommodation), financial invoicing, and will assist the team in the organization of activities with patients.

ERN CPMS Operational helpdesk: F. Ahssini, based in Belgium, Hôpital ERASME, is in charge of supporting ERN-EuroBloodNet members in the use of the CPMS and the customization of the platform according to ERN-EuroBloodNet needs.

The governance and coordination of ERN-EuroBloodNet is continuously supported by the activities of two functional structures: the Board of the Network (BoN) and Scientific and Strategic Board (SSB). In addition, an Independent Advisory Board has been established for seeking advice on specific issues.

Board of the Network (BoN)

The Board of the Network (BoN) is the decision-making body. It is chaired by the ERN coordinator and composed by the coordination team, all member representatives and ePAGs' representatives.

The main functions of the BoN are to:

- Attend Board meetings and represent their HCPs/associations
- Follow the rules of procedure established by the Board
- Pursue the Network's goals, objectives, and procedures
- Adhere to the Network's quality criteria
- Guarantee the smooth running of ERN-EuroBloodNet, oversee development of services and assess their impact.

In order to ensure the total and active enrolment of all members within the ERN-EuroBloodNet central gear, each member has designated one representative in the BoN and one substitute.

Scientific and Strategic Board (SSB)

The Scientific and Strategic Board (SSB) is composed by the coordination team members, the coordinators of the six subnetworks and the coordinators of the five transversal fields of action.

The main functions of the SSB are to:

- Define the multi-annual work plan (MWP) to ensure the achievement of ERN-EuroBloodNet objectives.
- Execute the BoN decisions and the operational implementation of the MWP.
- Assess the level of impact of outcomes.
- Ensure the outreach of results at the European and Member States levels.

Independent Advisory Board

An Independent Advisory Board (IAB) has been established from the outset involving European scientific associations representatives and experts on legal and ethical issues, epidemiological surveillance, education and external quality assessment.

IAB members defined during the 1st year of the network have been maintained during 2nd year and can be found at: https://www.eurobloodnet.eu/governance

Decision making process

Decision making process

Daily decisions have been taken by the coordination team and SSB providing the multi annual work plan is not affected by major changes.

Problems faced during tasks development have addressed according to their nature to:

- Heads of TFAs: when they affect directly the implementation of a transversal task.
- Sub-networks coordinators: when they affect the group of diseases involved in a given sub-thematic area.

In case a remedial action is not found, the issue has been escalated to the coordination team.

Communication

During the 1st period of the ERNs, the European Commission has provided ERNs with ERN Collaborative Platform (ECP) a specific platform for the internal communication of ERNs members. This restricted area has been very helpful for the sharing of ERN-EuroBloodNet internal documents as well as for the distribution of outcomes of the network. Webex system for teleconferences was also provided under request to the ECP support team.

In this context, communication has been established through four main means:

1) ERN Collaborative platform
2) E-mail or phone for daily matters and urgent questions
3) Both SSB and Board of Network meetings
4) Videoconferences when an extra meeting is needed – provided by ECP support team

BoN and SSB meetings

The BoN meets in a face-to-face meeting once a year, whereas the SSB meets every six months.

The ERN-EuroBloodNet coordination team organizes meetings to create and maintain the co-operation momentum, along well-defined targets, definining meeting locations and prepare the agenda, adhering to approved rules for decision-making and conflict resolution processes.

Activities undertaken specifically by ERN-EuroBloodNet coordination are included in section 1.7 Description of the activities carried per WP.

- Financial management

The ERN SGA Grant of the ERN-EuroBloodNet for year 2018, 811641, is supervised by Ms Gwénaëlle Gérard-Saigne, Head of The Research and Innovation Direction's Unit of Medical Business of the AP-HP hospital Saint-Louis « Cellule recherche & innovation Direction des Affaires Médicales, de la Recherche et de la Stratégie » of the hospital Saint-Louis, and its staff. This financial service of the hospital is in charge of the effective management of grant money: invoices paying purchase orders issuing, EuroBloodNet staff reimbursement, ERN-EuroBloodNet manager recruitment (staff costs including salary, social security contribution, taxis, other costs included in the remuneration).

The invoices produced by ERN-EuroBloodNet are checked by Miss Catherine Tostain Desmares, Head of the Europe Department (DRCI) Délégation à la recherche at the AP-HP Hospital Saint-Louis and Miss Nabila Llajail and Mr. Maxime Brun, Project managers in the European Department (DRCI) Délégation à la recherche at the Hospital Saint-Louis. Objective is to verify that the cost of the invoice is eligible by the EC SGA Grant.

Another financial role handle by DRCI European Department is the financial management of the invoices produced by University Hospital Vall d'Hebron – Vall d'Hebron Research Institute (HUVH-VHIR),Spain. This HUVH-VHIR has signed with the AP-HP hospital a Third-Party Agreement, when it figures as "second expert", in accordance to point 5.2 of the SGA regarding Direct personal costs and specifically for EuroBloodNet coordination, management and dissemination activities under the following premises:

- HUVH-VHIR and its seconded personnel will work under AP-HP's instructions;
- The result of the work carried out under the present agreement, belongs to AP-HP;
- The costs are not significantly different from those for personnel performing similar tasks under an employment contract with AP-HP.

Tasks carried out by HUVH-VHIR, are directly paid by AP-HP by bank transfer to HUVH-VHIR based on actual covering firstly, staff costs including salary, social security contribution, taxes, other cost included in the remuneration (if arisen from national law or employment contract) for the period between 1st March 2018 to 28th February 2019 + 2 months for the final reporting, as well as other expenses related to the organization of activities and meetings (travels and logistic) advanced by HUVH-VHIR.

HUVH-VHIR commits to make available to AP-HP supporting documents requested for staff costs justification as well as official timesheets for justifying allocation of personnel effort to the project. AP-HP commits to duly register staff costs in the institutional booking system for adequate justification of the costs to CHAFEA Subcontracted services have been managed following AP-HP rules in agreement with French Law.

1.2. Overview of the project results compared with the objectives of the action in line with the structure of Annex 1 to the Grant Agreement including summary of deliverables and milestones and a summary of project result. (No page limit per workpackage but report shall be concise and readable. Any duplication should be avoided)

This section contains results in relation with ERN-EuroBloodNet five specific objectives and linked Transversal Field of Actions (TFAs). Actions and milestones achieved concerning WP 1- Coordination and Evaluation and WP2 – Dissemination, are included in section 1.7 Description of the activities carried per WP.

All deliverables referenced in the report including full details on the activities performed and results, are public available at the ERN Collaborative platform and ERN-EuroBloodNet website.

WP 3 – TFA 1 – CROSS BORDER HEALTH

ERN-EuroBloodNet Specific Objective 1 linked to TFA1: Improve equal access to highly specialised healthcare delivery for RHD across Europe.

Task 1.1 Mapping of services (clinical and diagnosis) available in Europe for best clinical care

The main objective for the second year of network implementation were to expand and upgrade the European repository of ERN-EuroBloodNet experts and facilities implemented during first year of ERN-EuroBloodNet aiming to:

a) Upgrade of the technical solution for completion of ERN-EuroBloodNet members profiles and their visualization in the website

b) Exploit data gathered through the implementation of new tools

c) Expand the number of existing profiles to increase the evidence as the basis for Cross-border health

d) Establish the state of the art of Bone marrow transplantation and Next generation sequencing for non-oncological rare haematological diseases as highly specialized procedures in the context of ERN-EuroBloodNet

Accordingly, the following subtasks and results have been obtained:

1.1.1 Updates on the ERN-EuroBloodNet inventory of experts and members

ORPHA classification for RHD: Revision and update for Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis subnetwork

Diseases encompassed in the Hemochromatosis (HH) and other rare genetic disorders of iron metabolism and heme synthesis subnetwork are most of them very rare disorders that present an important gap in the classifications for rare diseases. In this context, while many of them are contemplated in the OMIM classification, there are still important gaps in their presence at the ORPHA classification.

As result of the ORPHA classification initial revision undertaken during first year of the network, 7 new codes related to HH and other rare genetic disorders of iron metabolism and heme synthesis subnetwork were created for their inclusion at the back office at the ERN-EuroBloodNet website. Nevertheless, discussion among experts have continued during this period in order to reach an agreement on the final consensus to be submitted to Orphanet and subsequently to ERN-EuroBloodNet website. Accordingly, an update on the first classification has been produced including the integration of porphyrias (defects of heme synthesis) and ferritinopathies (they are in the differential diagnosis of hypoferritinemias).

At this stage, discussions are still ongoing in order to create a consensus among experts, ie. Nomenclature issues under discussion by the "IBIS nomenclature commission", chaired by ERN-EuroBloodNet representative Domenico Girelli.

The second version of the ORPHA classification for HH and other rare genetic disorders of iron metabolism and heme synthesis subnetwork is currently being programmed for its availability in the ERN-EuroBloodNet website inventory.

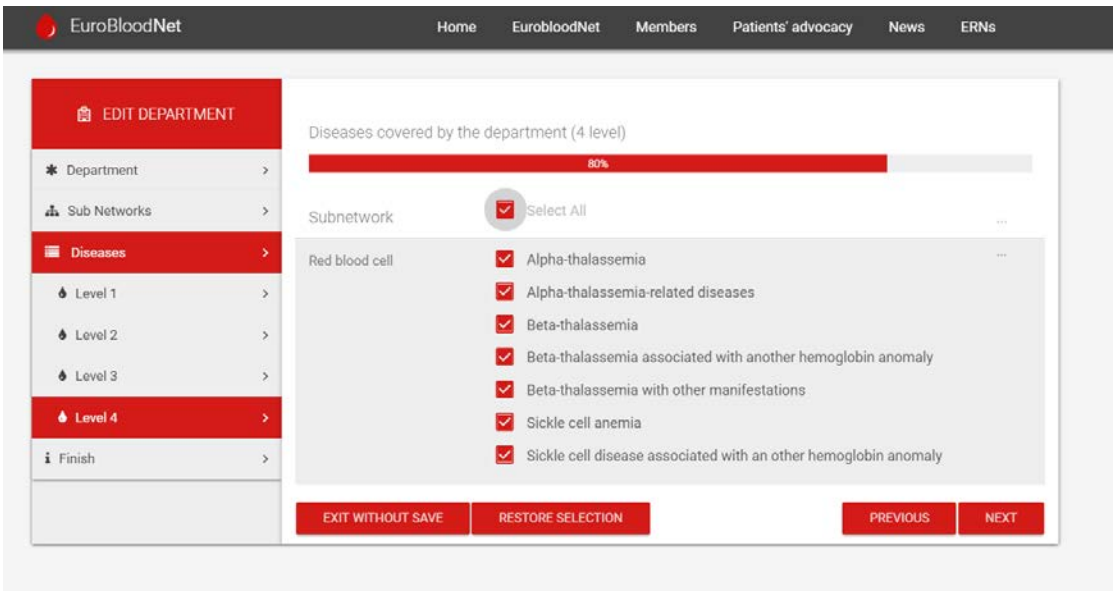
Improvement in the interface for the selection of diseases included in ORPHA classification

RHD ORPHA classification includes more than 450 different entities that are available in the ERN-EuroBloodNet website back office for their selection as a) diseases covered by the Departments, in the departments' profiles and b) diseases of expertise, in the Experts' profiles.

For the first release of the inventory, a tag system was chosen to select the diseases from the ORPHA classification. Based on the subnetwork selected, a group of diseases are shown in the first level. Then, based on this selection, diseases from the second level are listed… and so on until the fourth level.

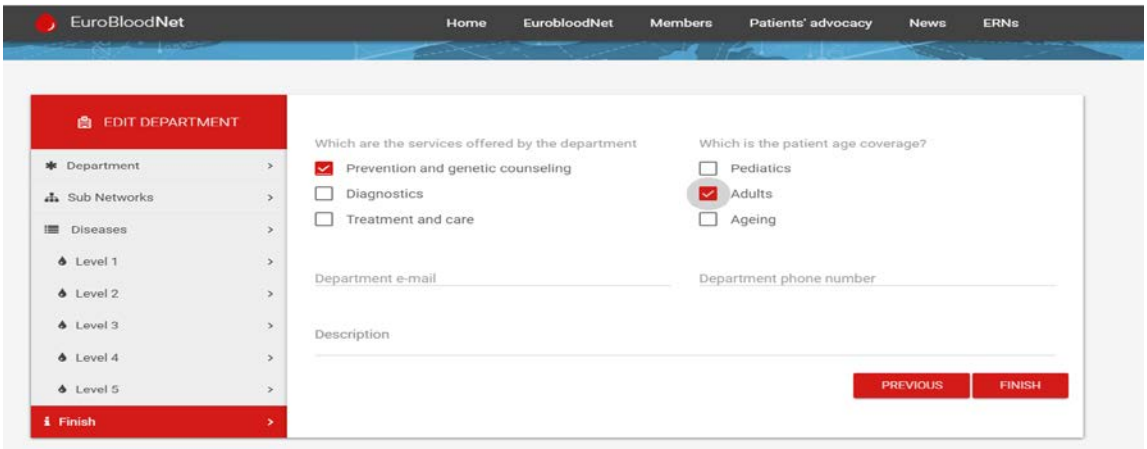
Nevertheless, given the high number of disorders to be selected, an improvement has been performed in the profiles application form for the selection of the diseases aiming to a) facilitate their selection by the experts and b) expand the possibility of the selection of the diseases through all the levels available at ORPHA classification.

To the date of this Report, the upgrade of the applications forms are not public, awaiting for the latest internal tests by the coordination team. The main upgrades in the application forms are:



For an easier selection of the diseases, diseases are shown based on the selection of the subnetworks and subsequent levels through the ORPHA classification. Diseases can be selected by clicking one by one or by clicking on “Select all”. In addition, the system will show at top of the diseases a bar with the % completed from the classification together with the level.

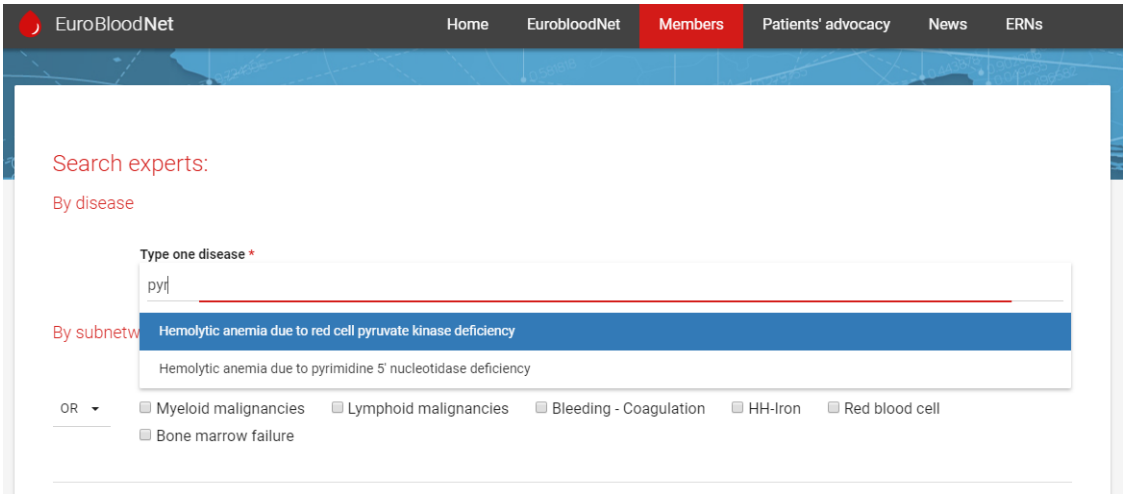
The interface will also apply to other information gathered regarding the services offered by the department or patients age coverage, as follows:



ERN-EuroBloodNet disease search engine

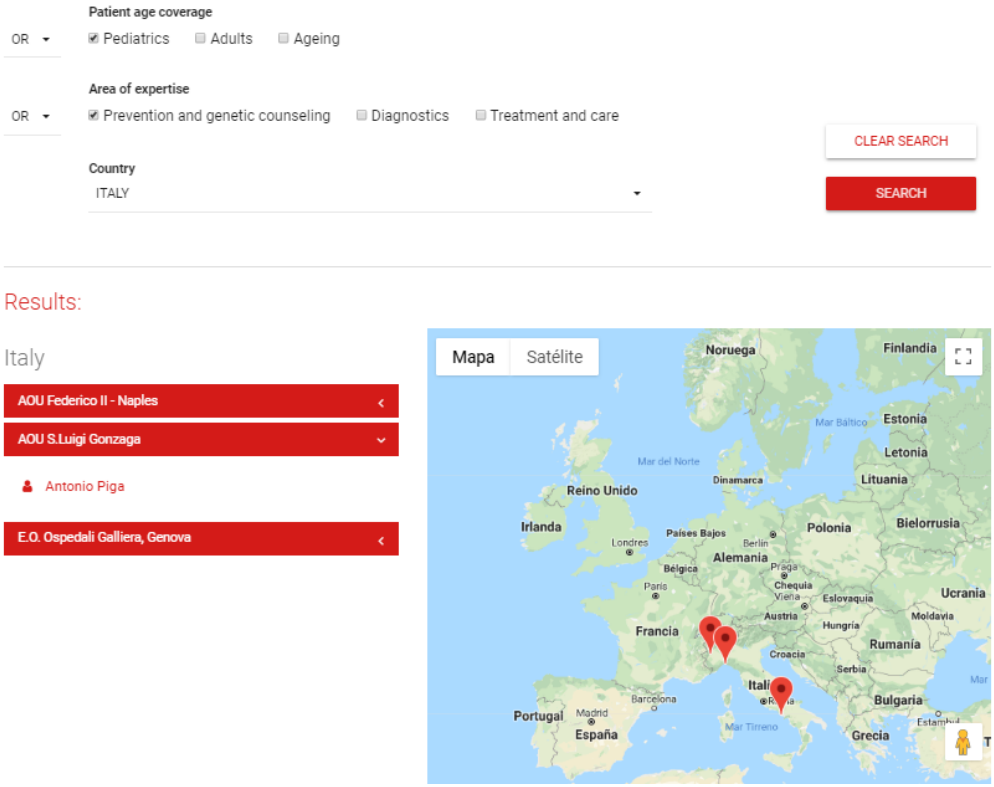
Disease Search tool (https://eurobloodnet.eu/search) has been implemented to exploit the data gathered through the inventory of ERN-EuroBloodNet members and experts.

The engine searches experts based on the information gathered through the Experts’ profile (not the disease/subnetwork the center deal with), offering the possibility of searching either by specific disease through the ORPHA classification, or by subnetwork. The search by the specific disease in the ORPHA classification is supported by an autocompleting tool that finds all the diseases in the classification including the letters typed:



The tool also includes different filters to add to the search as patients' age coverage, area of expertise, country. Moreover, filters provides the option to filter by "and" or "or", in order to include or exclude the selection in the search.

The search provides the experts that deal with the disease/s and filters selected by their centers and located in the map of Europe. Access to their personal profiles is directly available by clicking on the experts' names.



Public visualization of ERN-EuroBloodNet inventory at the website – Update

According to the new updates implemented in the ERN-EuroBloodNet inventory, the Members section accessible at the top bar of the ERN-EuroBloodNet website has integrated a submenu including "Member and representatives", "List of experts" and "Search experts".

Profiles information is accessible through ERN-EuroBloodNet website Members and representatives section. The table is linkable providing direct access to the Members profiles and Members' representatives and substitutes.

The design of the inventory ensures the linkage of all the information through the different profiles. Accordingly, experts profiles do not only provide the specific information related to experts' diseases and area of expertise, patient age coverage or role of the network but also provides a direct link to the Member, Healthcare provider and Department they belong to.

The list of experts section has been created in order to ensure the accessibility to all the individual Experts profiles created in the inventory, listed and directly available by clicking their names.

The search of experts by the disease search tool is also available through the button "Search experts".

Current state of the inventory

A total of 267 experts have already created their profiles in the ERN-EuroBloodNet directory, including both members representatives and substitutes and experts invited by them. 166 of them have fulfilled completely their profiles while the rest is in progress.

In general terms, it is remarkably the expansion of the ERN-EuroBloodNet inventory of members, not only in the total number of Experts' profiles correctly fulfilled with an increase of 70 new profiles, but also in countries with the creation of new profiles from Ireland and Sweden, countries that were previously lacking of profiles.

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	7	4	4
BG	1	1	
CY	13	13	
CZ	1		1
DE	3	1	3
ES	4	4	
FR	27	24	3
GB	14	10	4
IE	1	1	
IT	65	47	22
LT	2	1	1
NL	16	16	1
PL	4		4
PT	4	3	1
SE	4	4	
Total	166	129	44

Table 1. Number of experts by MS and hub

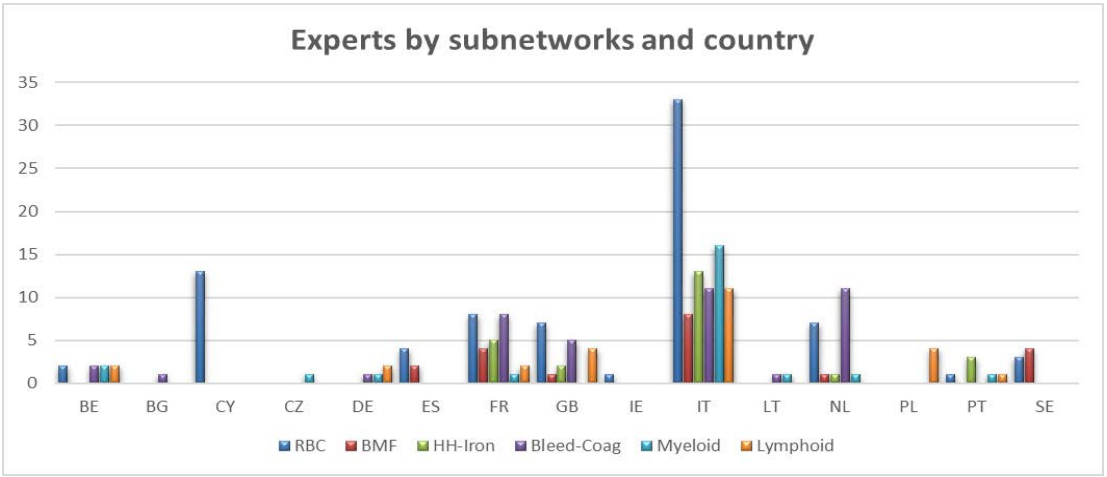


Fig 1. Number of experts by subnetwork and country. Subnetworks: Red blood cell disorders (RBC), bone marrow failures (BMF), Haemochromatosis and iron defects (HH-Iron), bleeding and coagulation (Bleed-Coag), Myeloid malignancies and lymphoid malignancies

Some differences can be observed among the oncological and non oncological hub attending to the area of expertise and patients' age coverage. Figure 2 shows the percentage of experts based on their expertise and hub. Figure 3 shows the percentage of experts dealing with children, adults or aged people by hub.

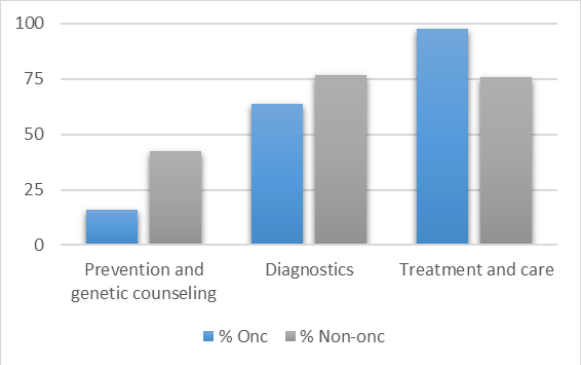


Fig 2 Percentage of experts by their area of expertise and dedicated hub

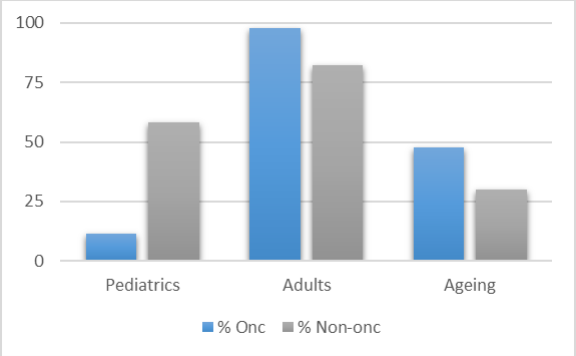


Fig 3 Percentage of experts by the patients' age dealing with and dedicated hub

Multidisciplinary teams are one of the cornerstones of the ERNs given the different approaches and fields of expertise that the management of rare diseases' patients requires. With the aim to compile useful information on the teams involved in ERN-EuroBloodNet, departments' profiles have been constituted as fundamental pieces of the net configuring the inventory of members.

In this context, departments are not only listed in the website, but have their full profile including the diseases covered, services offered, patients aged covered, experts involved…. Currently, a total of 225 departments linked to the members have been created in the ERN-EuroBloodNet inventory, representing 5 more than last year.

In addition, in order to create a smooth networking among the coordination and members, ERN-EuroBloodNet is trying to identify contact points in the specific sub thematic areas for each member in order to be directly involved in the specific tasks implemented by the network in their area of expertise. Accordingly, experts are requested in their individual profiles whether they are the representative person for any of the subnetwork/s in their healthcare providers.

At this stage, a total of 85 subnetworks representatives have been identified for 46 of the members.

Deliverable 3.1- Annual report on ERN-EuroBloodNet repository of experts and services for RHD includes the description of the implementation of the inventory and full results and analysis on ERN-EuroBloodNet's members' profiles, including data on the HCPs, experts, members of the multidisciplinary teams, diseases covered, age range and core facilities for health provision.

1.1.2 State of the art of Bone marrow transplantation and Next generation sequencing for non-oncological rare haematological diseases

As the basis for a cross-border health action, ERN-EuroBloodNet defines highly specialized procedures (HSP) as those procedures that for a number of reasons i.e. economical, lack of expertise or awareness, are not available in all EU-MS, thus preventing the delivery of the best care for EU citizens suffering from a RHD independently of their country of origin.

These HSP are classified as "under the scope" of the Directive 2011/24/EU if they are defined as standards of care and/or included in the national basket of health services for patients or "out of the scope" in the cases that they are still performed

on academic or experimental environment. In these cases, the European cooperation can be produced on the research field.

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 the context of ERN-EuroBloodNet, two priority HSPs have been identified for an action on the field of non-oncological haematological diseases: Bone Marrow Transplantation (BMT) and Next Generation Sequencing (NGS).

Two online surveys were conducted among ERN-EuroBloodNet members to analyse the state of the art of these two HSP with the main following results:

Bone Marrow Transplantation for non-oncological RHDs

A total of 27 centres from 13 member states (MS) answered que survey. Comparison between need for BMT per disease declared by the centres and availabilty of BMT is shown in Table 2.

Comparison BMT need / BMT availability			
	Need	**Availability**	**Difference**
SCD	70,4%	48,1%	22,2
THAL	74,1%	59,3%	14,8
METAB	48,1%	44,4%	3,7
AA	77,8%	74,1%	3,7
ID	51,9%	59,3%	-7,4

Table 2. Comparison between need for BMT per disease declared by the centres and availabilty of BMT
SCD: Sickle cell disorders, THAL: Thalassaemia syndromes, METAB: Metabolic Disorders, AA: Inherited or acquired aplastic anemia, ID: Immune Deficiencies

SCD is the condition for which the availability of BMT (48,1%) is the lowest, 22,2 points below the need (70,4%), followed by Thalassaemia syndromes in which availability of BMT (59.3%) is 14,8 points below the need (74.1%). In 7 centres which consider BMT for SCD patients, the procedure is not available, 5 of them belonging to the red blood cell subnetwork. From the 7 centres, 6 confirmed that they refer patients to another centre, 5 in the same country and one abroad. However, only 2 have a standardised procedure for referral of patients, being one of the two the centre referring patients abroad.

Next Generation sequencing for non-oncological RHDs

A total of 38 centres from 12 member states (MS) answered the survey.

Comparison between need for NGS/Advanced technologies declared by the centres and their availabilty is shown in Table 3.

Comparison NGS need / NGS availability			
Options	**Need**	**Availability**	**Difference**
Targeted NGS panels	100,0%	78,9%	21,1
Whole exome sequencing	62,9%	39,5%	23,4
Wide genome sequencing	17,1%	13,2%	4,0
Proteomics	11,4%	0,0%	11,4

Table 3. Comparison between need for NGS/Advanced technologies declared by the centres and their availability

The availability of the two HSP considered as more needed by centres, targeted NGS panels (78.9%) and whole exome sequencing (39.5%) respectively, is more than 20 points below the need, 21.1 for targeted NGS panels and 23.4 for whole exome sequencing. Less difference is resulting for wide genome sequencing, only 4 points below the need, showing that most of the centres considering it are those performing it. It is important to highligh that none centre perform proteomics.

Comparison between need for NGS/Advanced technologies declared by the centres and their availabilty by disease is shown in Table 4.

Comparison NGS need / NGS availability by disease			
Options	**Need**	**Availability**	**Difference**
Rare Anaemia Disorders	75,0%	62,5%	12,5
Coagulation disorders	41,7%	40,6%	1,0
Bone Marrow Failure Syndromes	52,8%	50,0%	2,8
Inherited or acquired aplastic anaemia	41,7%	37,5%	4,2
Immune Deficiencies	33,3%	34,4%	-1,0
Other	13,9%	12,5%	1,4

Table 4. Comparison between need for NGS/Advanced technologies declared by the centres and their availability by disease

Differences are observed mainly for rare anaemia disorders, for which availability (62.5%) is 12.5 points below need (75.0%). Differences in the other groups are less of 5 points, indicating that most of the experts on those conditions have access to NGS/advanced technologies in their own centres.

Deliverable 3.2 - State of the art of Bone marrow transplantation and Next generation sequencing for non-oncological rare haematological diseases in the context of ERN-EuroBloodNet reports the full results and analysis on the mapping of availability of highly specialized procedures for diagnosis, NGS, and treatment, BMT, of non-oncological hematologic disorders in the context of ERN-EuroBloodNet.

Milestone 8 Analysis of the questionnaire on the BMT/PKD across EU (Mo 4)

The milestone was modified based on HSP definition in the context of ERN-EuroBloodNet. The analysis of the dedicated questionnaires was performed accordingly on BMT and NGS during month 10 (see also 1.1. Reasons for deviations from Annex 1).

Task 1.2. Establishment of a model for cross border referral system - Directive 2011/24/EU

In the frame of ERN-EuroBloodNet, a Collaboration agreement for Crossborder Health (CBH) on BMT for Sickle Cell Disease (SCD) pediatric patients has been launched between a member from Italy and other one from Ireland, while a second agreement is being initiated for BMT on SCD for adults between a member from France and another from Belgium.

The establishment of the collaboration between Italy and Ireland has shown key hot points for its implementation, including the clinical protocol, administrative burden, legal framework and logistics and specially reimbursement scheme.

A dedicated task force has already been established for the definition of a working plan aiming to create a CBH toolbox to a) facilitate the establishment of future agreements for CBH on highly specialized procedures b) provide the evidence required as the base for discussion by the MS to enhance the political implication in the field.

1.2.1 Definition of task force

A dedicated task force has been defined:

- Raffaella Colombatti – TFA on CBH coordinator for the non-oncological hub
- Ananda Plate – TFA on CBH coordinator, ePAG representative for Myeloid disorders
- Loris Brunetta – ePAG representative for Red blood cell disorders
- Pilar Nicolás – Legal expert, Independent Advisory Board
- María del Mar Mañú – Scientific director
- Victoria Gutiérrez – IT and dissemination manager
- Mariangela Pellegrini – ERN manager

1.2.2 Action plan for the creation of a CBH toolbox

The plan defined includes the analysis of the Collaboration agreement for BMT on SCD among Italy and Ireland for the identification of the critical and most conflictive issues for its establishment and its translation into a practical tool that will include:

- Key actors involved in the process
- Roadmap and timing
- Challenges found from the medical, administrative and financial point of view
    - Clinical coordination
    - Clinical protocol
    - Administrative burden
    - Costs analysis and reimbursement procedures
- Identification of the variables that can be adapted at the National level impacting on the establishment of CHB agreements according to the national regulations

- Analysis of variables in:
  1. Italy, Ireland
  2. France, Belgium
  3. Other MS to be defined

Milestone 9 Legal analysis of EU laws regulating cross border health (Mo 12)

Directive 2011/24/EU on patients' rights in cross-border healthcare establishes the rights for every EU citizen to receive medical care in another Member State and to be reimbursed for care abroad by their home country, allowing patients to access to the best expertise and most appropriate treatment available, even if not available in their own countries.

The Directive provides a common law at EU level that is transposed by each MS. In this transposition at the national level, there is room for different interpretations of the Directive by each of the MS, providing space for modifications in its implementation among countries.

Additional Regulations (laws mandatory for all MS) have to be contemplated in the CBH procedures, as the one regulating the agreements among social security systems in the public systems.

The identification of the variables that can be adapted at the National level impacting on the establishment of CHB agreements according to the national regulations is already ongoing as key point on the action plan for the CBH toolbox. Legal analysis will continue in the upcoming period of ERN-EuroBloodNet implementation.

WP 4 – TFA 2 – BEST PRACTICES

ERN-EuroBloodNet Specific Objective 2 linked to TFA2: Promote best practice in prevention, diagnosis and clinical care across EU

Task 2.1. Create a comprehensive public database of reliable guidelines

2.1.1 Expansion of the List of international guidelines and recommendations

The list of international guidelines and recommendations was successfully reviewed and expanded including a total of 117 Clinical Practice Guidlines (CPGs) for the six subnetworks. See Figure 4.

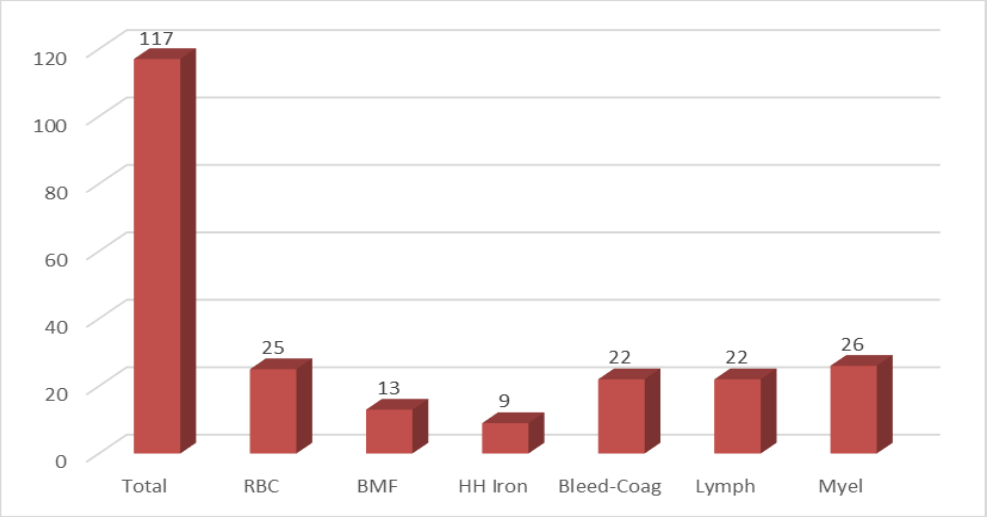


Fig 4. List of international guidelines/recommendations compiled for RHD (RBC: Red blood cell diseases subnetwork, BMF: Bone marrow failures subnetwork, HH-Iron: Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis subnetwork, Bleed-Coag: Bleeding and coagulation subnetworks, Lymph: Lymphoid malignancies subnetwork, Myel: Myeloid malignancies subnetwork.

2.1.2 Classification of guidelines and recommendations based on Quality domains

A methodology for classification of guidelines and recommendations based on Quality Domains was defined according to three domains: Scope and purpose, patients' involvement and Rigour of development.

A total of 24 guidelines/recommendations for RBC, 13 for BMF, 6 for HH-Iron and 26 for Myeloid were classified based on quality domains with the participation of 10 ERN-EuroBloodNet experts. The task is still ongoing for the Bleeding and coagulation disorders and Lymphoid malignancies. Figures 5, 6 and 7 reports the classification on the domains for the four subnetworks analysed.

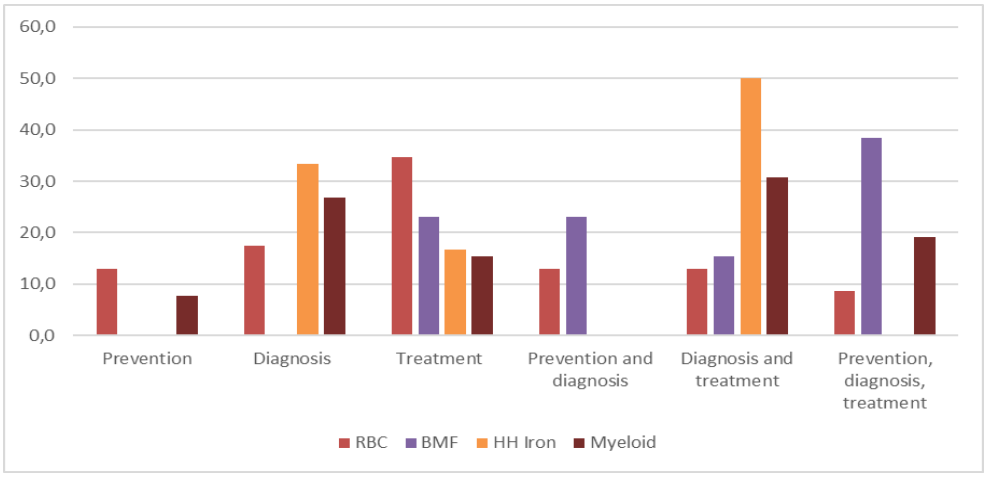


Fig 5. Comparison among subnetworks on % Guidelines/recommendations based scope and purpose

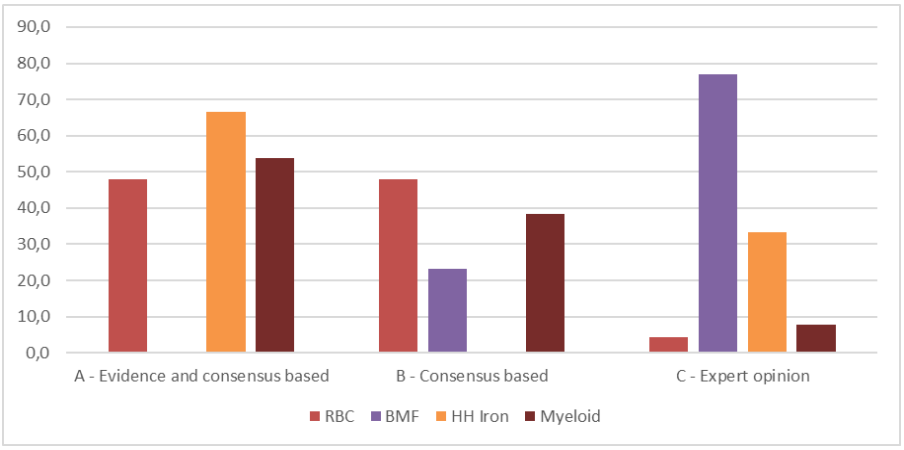


Fig. 6 % Guidelines/ recommendations based on rigour of development

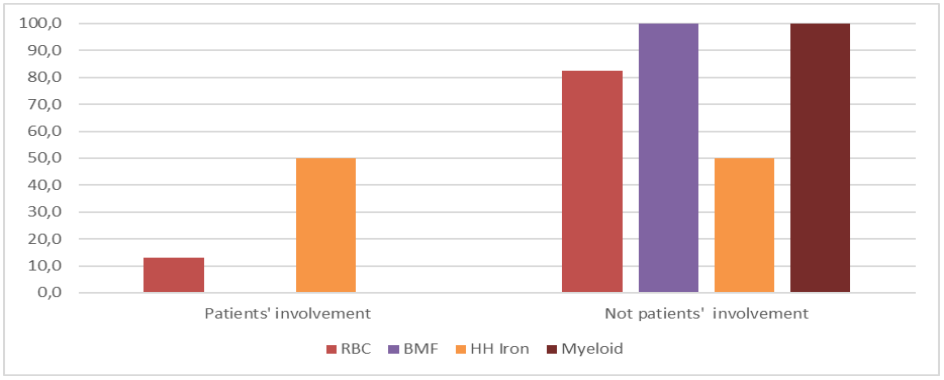


Fig 7. % Guidelines/recommendations based on patients' participation

The exercise has shed light on the current coverage of CPGs for four of the subnetworks while allowing the identification unbalances among the different scopes and purposes.

In addition, a clear need of patients' involvement in the generation of CPGs have been revealed, especially in the Myeloid, bone marrow failures and red blood cell disorders areas, where their involvement have been null or nearly null in the CPGs assessed.

The analysis of the classification attending the rigour of development has also provided very valuable information of the grade of evidence used for their creation, while allowing the identification of areas where additional efforts are needed to increase the CPGs available as level A, for instance, on the bone marrow failures area.

Deliverable 4.1 Report on the comprehensive public database of reliable guidelines includes the description of the full methodology followed for the expansion of the list of international guidelines and recommendations and their classification based on Quality Domains. Main results and analysis of the classification are also reported.

Milestone 10 Report on the comprehensive public database of reliable guidelines (Mo 12)

The report was successfully submitted by December 2018.

Task 2.2. Assessment of the level of awareness and implementation of existing guidelines

2.2.1 Diseases and indicators identified for assessment of the holistic clinical management of RHD conditions including prevention, diagnostic tests, treatment and follow up.

As first step in the assessment process, it was agreed to identify key indicators for the assessment of guidelines/recommendations awareness and implementation. Since ERN-EuroBloodNet encompasses more than 450 disorders of wide heterogeneity on their clinical coverage and needs, the first actions defined were the identification of:

- Concrete guidelines/recommendations addressing specific disorders which, due to multiple reasons, are expected to be poorly implemented in MS.
- Clinical outcome indicators having some pointing to the minimal requirements (standard of care) and/or related to highly specialized procedures. Indicators should ideally cover several areas as prevention, diagnosis, clinical care and follow up

The first round of answers gathered a total of 4 selected disorders to assess related guidelines implementation from 3 different subnetworks, specifically concerning to:

- Sickle Cell Disease - Red blood cell subnetwork
- HFE- Haemochromatosis - Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis subnetwork
- Anemia due to genetic disorders of iron metabolism and heam disorders - Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis subnetwork
- Myelodysplastic syndromes - myeloid malignancies subnetwork

2.2.2 Assessment of the implementation of the Consensus recommendations on the diagnosis of pyruvate kinase deficiency (PKD)

Pyurvate Kinase enzyme assay for the diagnosis of PKD has been identified as a routine test commonly misinterpreted or lacking at the European level, leading to an underestimation of the real number of patients. ERN-EuroBloodNet has recently endorsed the "Addressing the diagnostic gaps in pyruvate kinase deficiency: Consensus recommendations on the diagnosis of pyruvate kinase deficiency" for the promotion of timely and appropriate diagnosis. A practical exercise of assessment of its implementation is being performed based on two approaches:

a) Mapping of centers performing PKD diagnosis and facilities for accurate diagnosis and genetic characterization

In order to identify centers performing PK diagnosis and core facilities, a survey was conducted among ERN-EuroBloodNet members and 40 medical centers not members but previously involved in PKD actions. A total of 41 medical centres from 10 countries completed the survey.

Based on the results, a total of 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 diagnosis per year. Distribution of results on activity by country is shown in Table 5 and Figure 8.

Distribution Patients and diagnosis	Medical Centres	Patients in follow up	Patients Genotyped	% Patients Genotyped	PKD Diagnosis
Belgium	4	8	7	87,50%	21
Czech Republic	1	6	3	50,00%	10
France	5	115	111	96,52%	117
Germany	4	14	14	100,00%	7
Italy	9	42	38	90,48%	133
Netherlands	4	26	23	88,46%	138
Portugal	1	11	11	100,00%	30
Spain	8	20	12	60,00%	22
United Kingdom	2	18	12	66,67%	3
Total	38	260	231	88,85%	481

Table 5. Distribution of activity by country

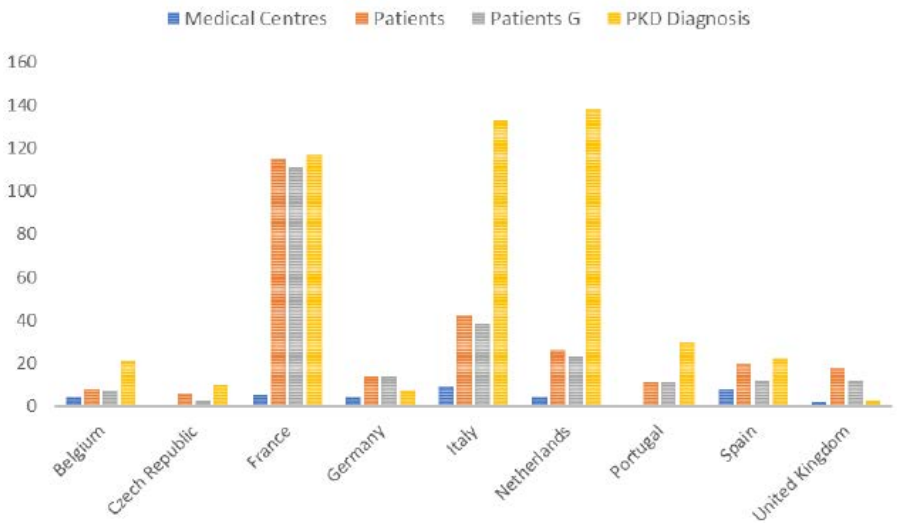


Fig. 8 Distribution of activity by country

b) Establishment of the External Quality Assessment on PK diagnosis in collaboration with UKNEQAS

The External Quality Assessment (EQAs) for PK diagnosis is currently being undertaken in a pilot phase. First pilot phase involves 9 laboratories from 4 countries (UK – 4 laboratories, Spain – 2 laboratories, Italy – 1 laboratory, Netherlands – 2 laboratories). It has been requested quantitative assay values, with reference range. In addition, also interpretation of results along with the clinical context will be requested to participants.

More laboratories will be included in a second phase during Q1 2019.

Deliverable 4.2 Report on guidelines implementation details the full methodology followed for the gathering of indicators for guidelines/recommendations implementation assessment as well as main results.

Milestone 11 Report on guidelines needed to be addressed by the EHA working group (Mo 10)

A first analysis of areas where guidelines and recommendations have to be promoted is included in Deliverable 4.1 Report on the comprehensive public database of reliable guidelines. The classification of the documents compiled based on Quality Domains has provided very valuable information on areas remained uncovered by any guidelines or recommendations, or that need to increase the rigour of development based on the evidence.

While the assessment of guidelines and recommendations implementation is ongoing, ERN-EuroBloodNet and the European Hematology Association (EHA) maintains a close collaboration for all the activities concerning best practices and especially in the area of guidelines and recommendations, where TFA coordinators (L Malcovati and A Iolascon) are also representatives at the EHA guidelines working group ensuring the synergies among both groups.

WP 5 – TFA 3 – CONTINUING MEDICAL EDUCATION

ERN-EuroBloodNet Specific Objective 3 linked to TFA3: Disseminate cutting-edge knowledge and facilitate continuing medical education in the field of RHDs

Task 3.1. Identification of educational GAPs survey in collaboration with EHA

3.1.1 ERN-EuroBloodNet questionnaire on Continuing Medical Education

A questionnaire was conducted among ERN-EuroBloodNet members in order to a) compile educational material for professionals or patients and b) identify and assess the educational needs within the network. A total of 21 answers compiling feedback from 27 experts were received from ERN-EuroBloodNet members belonging to 9 European Member States.

A total of 152 educational materials were compiled and classified according the criteria assigned in the template. The coverage of the material compiled by subnetwork is illustrated in figure 9, while the target of the material by the subnetwork is reported in figure 10.

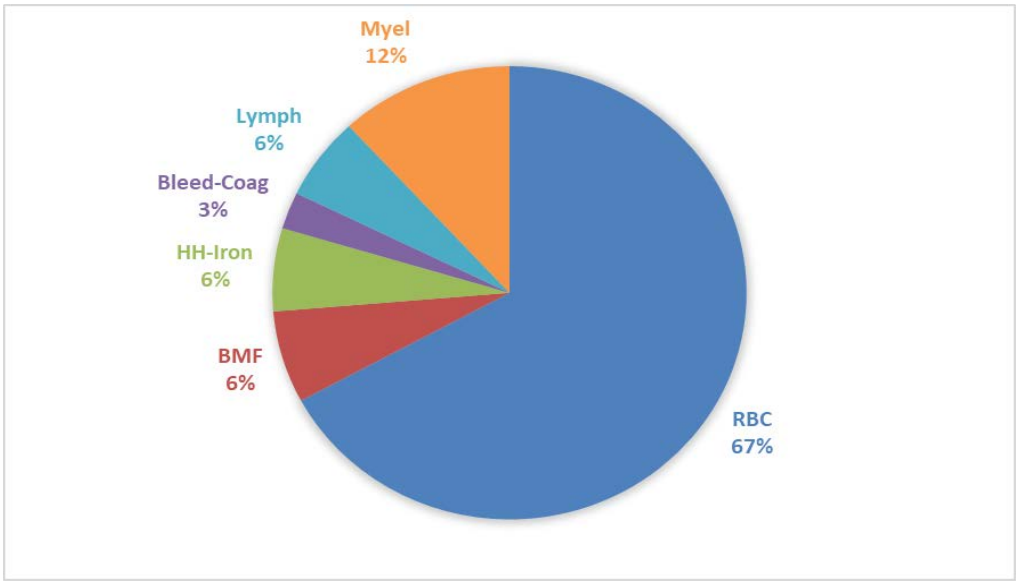


Figure 9. Coverage of the Educational material compiled through the ERN-EuroBloodNet questionnaire on CME by subnetwork (RBC: red blood cell defects, BMF: Bone marrow failure and hematopoietic disorders, HH-Iron: Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis, Bleed-Coag: Rare bleeding-coagulation disorders and related diseases, Lymph: Lymphoid malignancies, Myel: Myeloid malignancies).

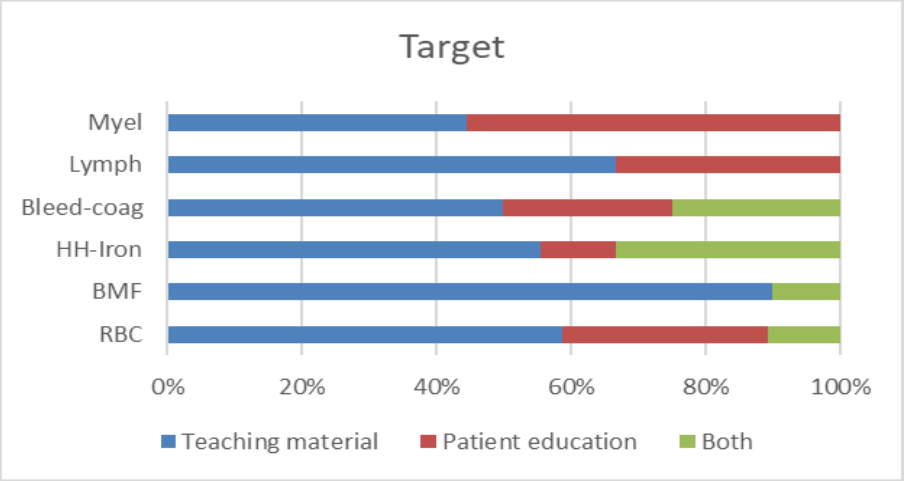


Fig 10. Target of the Educational material compiled through the questionnaire on CME by subnetwork

Some of the most important gaps identified through the compilation of material are:

- Low/Lack of material available for patients focused on erythroenzymopathies, RBC membrane defects and erythrocytosis
- Almost the total lack of material addressed to patients for Bone marrow failures subgroups. In addition, Pearson Syndrome is specially poorly covered by educational material for health professionals
- Lack of material for patients' education on the Gaucher Disease
- Lack of material for patients on Rare hemorrhagic disorders due to a platelet anomaly
- Evident need for generating material for patients' education for the lymphoid disorders, with the exception of ALL and CLL, and for the myeloid disorders, specially for CMML and Acute promyelocytic leukaemia.

In addition, the gathering of the educational needs has allowed the identification of the following requirements on teaching material for:

- NGS based diagnosis and Proteomics for haemoglobinopathies
- Diagnosis and clinical management of Enzymopathies, Membranopathies and other Hemoglobinopathies (except Thal and SCD)
- Diskeratosis congenital, Blackfan Diamond Anemia, Amegacaryocytic thrombocytopenia
- Iron chelating drugs in MDS and "atypical microcytic anemias" with iron overload
- Plasmoblastic lymphoma, granuloma, diffuse large B-cell lymphomas, HS lymphomas.
- MDS in genetic risk, assessment and diagnostics

3.1.2 Repository of Sickle Cell Disease Therapeutic Patient Educational material

Up to now, SCD is one of the rare anemias that does not have, in every country in Europe, an adequate educational contribution to daily management of the disease. SCD is indeed traditionally endemic in African and Middle East countries but their frequency has increased recently in Europe due to migration and mobility flows. So, the therapeutic educational needs of the SCD patients is not explicitly covered, since the awareness level of the disease and the presence of the patients organizations at

the national level are extremely varied from country to country, and they could face, in most cases, many integration difficulties of a population largely coming from third countries, as for instance to have access to cares and to assert social rights.

Accordingly, ERN-EuroBloodNet is currently identifying the SCD patients' needs across European Member States in order to better analyze the existing gaps and try to face them through dedicated actions.

A parallel Questionnaire on the available educational material for SCD patients has already been defined with the objectives to:

- Expand the educational material available compiled via the questionnaire on continuing medical education (3.1.1)
- Collect patients' opinion about the therapeutic patient educational domains to be covered.

Questionnaire will be translated and conducted in the next period of network implementation.

Deliverable 5.1 Report on educational gaps includes the full repository of educational material and analysis of the gaps identified together with additional educational actions undertaken during this period of implementation.

Milestone 12 Launch of the survey on educational GAPs (Mo 3)

Questionnaire on Continuing medical education was successfully conducted from July to September 2018.

New Task 3.2 Webinars program for health professionals

ERN-EuroBloodNet has defined a Webinar program with the aim to contribute to continuing medical development requirements of health professionals, assisting them to provide cutting-edge knowledge on very rare diseases and highly specialised procedures, avoiding the general speech around a rare disease, but focussing on a very innovative and specific disease, clinic or intervention area.

Each Webinars will last 45 minutes: 30 minutes for the expert's presentation and last 15 minutes for hearers' questions. In addition, they will be held always in the same day of the week and time slot (foreseen Thursdays at 17:00).

ERN-EuroBloodNet will implement 1-2 webinars per month. The balance among subnetworks will be ensured, holding 2-4 webinars/year/subnetwork.

Deliverable 5.1 Report on educational gaps includes the draft list of 16 educational webinars and potential speakers

Task 3.3. Co-organization with the ePAGs of European symposia with interactive patient participation

The "EHA Capacity Building Meeting" organized by ERN-EuroBloodnet , ePAGs and the Hematology ePAG Project Management Office, within the 23rd EHA congress took place Thursday, the 14th of June 2018, between 2 pm and 5 pm. The meeting was successfully held with a total of 69 attendants.

Milestone 14 Report on European Symposium - 23rd EHA congress in Stockholm June 14-17, 2018 (Mo 6)

Milestone achieved on due time. Details of the program are included in "Deliverable 5.1 Report on educational gaps"

Task 3.4. Identification of areas including highly specialized procedures requiring short stays for the acquisition of expertise

During first year of ERN-EuroBloodNet implementation Paroxysmal nocturnal hemoglobinuria (PNH) Aplastic Anemia (AA) were identified as one are to be benefited from the organization of short stays due to the lack of expertise in its diagnosis, leading potentially to a worsen of prognosis on the health's patient.

During this period the three highly specialized centers hosting fellows as well as concrete agendas, teachers and focussed topics to be covered by each center has been defined.

The call for participants will be open in the coming period of network implementation.

Milestone 15 Report of short stays on PNH

The full objectives, plan, topics and teachers for each site have already been defined and included in "Deliverable 5.1 Report on educational gaps" and its "Annex III AA and PNH Precerptoship program"

WP 6 – TFA 4 – Telemedicine

ERN-EuroBloodNet Specific Objective 4 linked to TFA4: Provide inter-professional consultation by sharing of expertise and safe exchange of clinical information

Task 4.1. Pilot testing of the CPMS

CPMS pilot testing took place from November 2017 to March 2018. In this pilot stage ERNs were requested to participate in order to detect potential improvements to be corrected in the next months.

A total of 12 ERN-EuroBloodNet experts participated in the pilot phase, with the enrolment of 6 patients.

A feedback questionnaire was circulated among participants and a report was provided to the EC including the answers received.

Deliverable 6.1 Report on CPMS activity by ERN-EuroBloodNet members includes the results from the participation in the CPMS pilot phase.

Milestone 16 CPMS Pilot phase feedback from first users (Mo 1)

A report was provided to the EC including the feedaback received from the pilot users in March 2018, included also in "Deliverable 6.1 Report on CPMS activity by ERN-EuroBloodNet members".

New Task 4.2 ERN-EuroBloodNet strategy for promoting the wide implementation of the CPMS

In order to ensure an efficient and effective implementation of the CPMS, an ERN-EuroBloodNet strategy for the promotion of the use of CPMS was defined including:

4.2.1 CPMS promotion and awareness among members

Dedicated efforts have been focused on increasing the awareness on the CPMS and its rationale between healthcare professionals community in order to increase the number of users ensuring full disease and country coverage. As a result of the CPMS promotion, the state of the art of the CPMS is the following:

a) Numbers of panels

A total of 12 panels have been opened for RHDs since the launch of the CPMS. Table 6 summarizes the number of cases introduced per thematic area and advice required

Thematic area	Diagnosis	Treatment	Diagnosis and treatment	**Total**
Haemoglobinopathy	1		1	**2**
Hereditary erythroenzymopathies and RBC membrane defects	2			**2**
Congenital dyserythropoietic anemia, Blackfan-Diamond anemia, Acquired BMF and Inherited BMF	2	1		**3**
Myelodysplastic syndrome (MOS)		2	2	**4**
Rare lymphomas		1		**1**
Total	**5**	**4**	**3**	**12**

Table 6. Panels by thematic area and advice required

b) Number of CPMS account created for the EuroBloodNet ERN members

The number of haematological experts who have a CPMS account increased from 12 (March 2018) to 55 (February 2019).

4.2.2 Upgrade of RHD categories in the “Preferences” section

ERN-EuroBloodNet identified the upgrade of the RHD classification available in the “Preferences” section as the first action to be performed for ensuring its efficient use:

Disease Categories

ERN-EuroBloodNet CPMS helpdesk and coordination team prepared a new proposal of disease categories for each subnetwork based on ORPHA classification to be discussed and agreed among subnetworks experts.

A total of 6 experts participated in the first analysis of the preferences upgrade while provided their views of CPMS needs in the different categories, including an assessment of the type of advice and age of patients for which the CPMS is most required.

New category for highly specialized procedure - Bone Marrow Transplantation for oncological and non ongological disorders

The expertise required for the performance of BMT is highly disease-specific dependent in the RHD area. Accordingly, a new category will be proposed to be included in the CPMS preferences for non oncological and oncological disorders.

The feedback on this new category is ongoing so a future analysis will be undertaken in the next period of the network.

Deliverable 6.1 Report on CPMS activity by ERN-EuroBloodNet members includes all the actions performed on the strategy for promoting the wide implementation of the CPMS and the results, including the analysis of the CPMS needs and upgrade of the “Preferences section”.

WP 7 – TFA 5 – Clinical Trials and Research

ERN-EuroBloodNet Specific Objective 5 linked to TFA5: Foster European cooperation in highly specialised procedures for diagnosis, innovative treatments and research

Task 5.1. To facilitate European epidemiological surveillance of RHD by promoting the creation of a European registry of patients affected by a RHD

ERN-EuroBloodNet covers up to 450 RHD which present with prevalences ranging from 0,049% to 10^-7%, meaning from 1 patient affected out of 2.032 individuals to 1 patient affected out of 101.600.000 individuals. With this scenario, the setting up of a central European registry covering all RHD need to contemplate different strategies for a comprehensive approach.

Accordingly, prevalences for the main groups of RHD have been reviewed and classified according to the following criteria (Table 7):

- Ultra-rare RHD: prevalence equal or less than 1/50.000
- Prevalent RHD: prevalence equal or more than 1/10.000
- Rare RHD: more than 1/50.000 and less than 1/10.000

Rare Hematological Disease or group of diseases	Prevalence (%)	Prevalence (1/x)
Acquired BMF (Aplastic Anaemia and PNH)	0,000886%	112.889
Acute lymphoblastic leukemia (ALL)	0,003000%	33.333
Acute myeloid eukemia (AML)	0,006000%	16.667
Blackfan-Diamond anemia	0,000217%	461.818
Chronic Myeloid Leukemia (CML)	0,010000%	10.000
Chronic myelomonocytic leukemia (CMML)	0,002500%	40.000
Congenital dyserythropoietic anemia	0,000197%	508.000
Congenital Erythrocytosis	0,000689%	145.143
Defects in heme synthesis or Fe-S cluster biogenesis	0,000059%	1.693.333
Defects in iron acquisition, transport: IT, DMT1, STEAP3	0,000001%	101.600.000
Haemoglobinopathy (SCD, Thalassaemia, [other Hbpathies)	0,035433%	2.822
Haemophilia A and B (including female carriers)	0,014764%	6.773
Hairy cell leukemia	0,001800%	55.556
Hereditary (RBC) erythroenzymopathies	0,001000%	100.000
Hereditary RBC membrane defects	0,028583%	3.499
HFE-related hereditary hemochromatosis	0,000004%	25.400.000
Hodgkin Lymphoma	0,017500%	5.714
inherited BMF (FA, Dyskeratosis congenital, others)	0,000089%	1.128.889
Inherited platelet defects	0,000197%	508.000
Light chain Amyloidosis (AL amyloidosis)	0,001000%	100.000
Low iron availability or erythropoiesis: RIDA, ACP	0,000027%	3.762.963
Marginal zone lymphomas	0,005000%	20.000
Mlyelodysplastic Syndrome (MDS)	0,010031%	9.969
Myeloproliferative neoplasm (MPN)	0,040000%	2.500
non-HFE related lereditary lemochromatosis	0,000098%	1.016.000
Primary CNS lymphoma*primary vitro retinal lymphoma	0,001299%	76.970
Primary myelofibrosis	0,001200%	83.333
Rare Lymphoma follicular lymphoma	0,032000%	3.125
Rare Lymphoma Mantle cell lymphoma	0,001800%	55.556
Rare Lymphoma Primary cutaneous lymphomas	0,003000%	33.333
Rare Lymphoma Virus associated lymphomas	0,002500%	40.000
Systemic mastocytosis	0,000200%	500.000
The rarer congenital deficiencies of other coagulation factors	0,000787%	127.000
Von Willebrand	0,049213%	2.032

Table 7. Classification for the main groups of RHD according to prevalences range.

The ERN-EuroBloodNet central European registry will cover all RHD with a first phase of implementation restricted to ERN–EuroBloodNet official members and affiliated partners.

The platform objectives will be:

a) Estimation of the Incidence / prevalence at the EU level and Member State of the different RHD based on data from members + affiliated and literature review
b) Disease survival
c) Time for diagnosis
d) Time for referral to the member / affiliated
e) Genotype
f) Availability of biological sample
g) Disability profile
h) Stratification of patients based on severity and response to treatment

Accordingly an extended common data set will be produced based on the core list of 18 items produced by the EU-RD-Platform https://eu-rd-platform.jrc.ec.europa.eu/

The European Rare Disease Registry Infrastructure (ERDRI) renders rare disease registries' data searchable and findable. This is achieved through the provision of following components: European Directory of Registries (ERDRI.dor), Central Metadata Repository (ERDRI.mdr), Pseudonymisation Tool (EUPID).

Accordingly, the registry will be created in line with the EU-RD-Platform and will incorporate the use of EUPID. EUPID is designed to provide distinct pseudonyms for patients in different contexts, prevent duplicate registration of patients, keep a protected link between the different pseudonyms and preserve the possibility for re-identification by a trusted third party.

Different approaches will be established for the gathering of data based on disease prevalence and structure of the national health systems. A mapping exercise will be conducted to assess how RHD are codified in the electronic health records of ERN-EuroBloodNet members and affiliated.

Finally, guidelines will be produced for ensuring interoperability with other European initiatives for patients' registries and / or –OMICs platforms, as RADeep, the Rare Anaemia Disorders European Epidemiological platform.

RADeep is an initiative conceived by mostly ERN-EuroBloodNet partners endorsed by both ERN-EuroBloodNet and the European Hematology Association (EHA) aiming at promote clinical and basic research at the European level on rare anaemia. RADeep principle is to open-up existing and new databases on patients affected by rare anaemias with the only restriction needed for guarantying patients' rights according to the new regulation on data protection. Accordingly, ERN-EuroBloodNet promotes the participation of expert centres and national registries in RADeep and ensures the application of recommendations released by the EU-RD-platform.

Milestone 19 Report on registry initiatives promoted by ERN-EuroBloodNet (Mo 12)

Milestone partially achieved. A first analysis of the different strategies to be implemented for the establishment of a central European registry covering all RHD has been undertaken based on the different prevalence of the diseases tackled by the network. In addition ERN-EuroBloodNet has promoted the participation of expert centres and national registries in RADeep while ensuring the application of recommendations released by the EU-RD-platform. In this context, agreements has been established for the participation in RADeep of:

- Spanish registry for SCD and Thalassaemia patients
- French registry for thalassaemia patients
- French registry for pyruvate kinase deficiency patients

- German registry for SCD patients

A report will be produced once the central European registry on RHD is implemented.

Task 5.2 To promote the participation in clinical trials

Two main actions have been undertaken for the promotion of participation of CTs:

5.2.1 Analysis of the state of the art of on-going CTs for rare hereditary anaemias

In order to establish the state of the art of on-going CTs for rare hereditary anaemias (RHAs) a desk research was conducted on ClinicalTrials.gov website.

122 "Search terms" covering 105 disorders classified as rare hereditary anemias were established based on ORPHA classification. A total of 256 CTs resulted from the analysis after removing duplications and assess quality of data regarding disease focus. Results are included in table 8 and figure 11

CTs "Rare Hereditary Anemias" Search terms	256	
Without focus on a concrete condition	**24**	**9.4%**
Rare hematological disorders (RHD)	10	3,9%
Oncological RHD	3	1,2%
non-Oncological RHD	10	3,9%
Hemolytic anemia	1	0,4%
With focus on (a) concrete condition (s)	**232**	**90.6%**
Sickle cell disorders	155	60,5%
Thalassemia	53	20,7%
Pyruvate kinase deficiency	3	1,2%
Muscle phosphofructokinase deficiency	2	0,8%
Blacfand Diamond Anemia	2	0,8%
Fanconi Anemia	16	6,3%
Pearson syndrome	1	0,4%
Congenital erythropoietic porphyria	2	0,8%
Dyskeratosis congenita	2	0,8%
Shwachman-Diamond syndrome	1	0,4%
Hoyeraal-Hreidarsson syndrome	1	0,4%
Revesz syndrome	1	0,4%
Monocytopenia with susceptibility to infections	1	0,4%
Congenital atransferrinemia	1	0,4%
Drugs	**103**	**40,2%**
Bone marrow transplant	**72**	**28,1%**
Gene Therapy	**21**	**8,2%**
Other	**60**	**23,4%**

Table 8 – List of CTs and breakdown according to disease and intervention

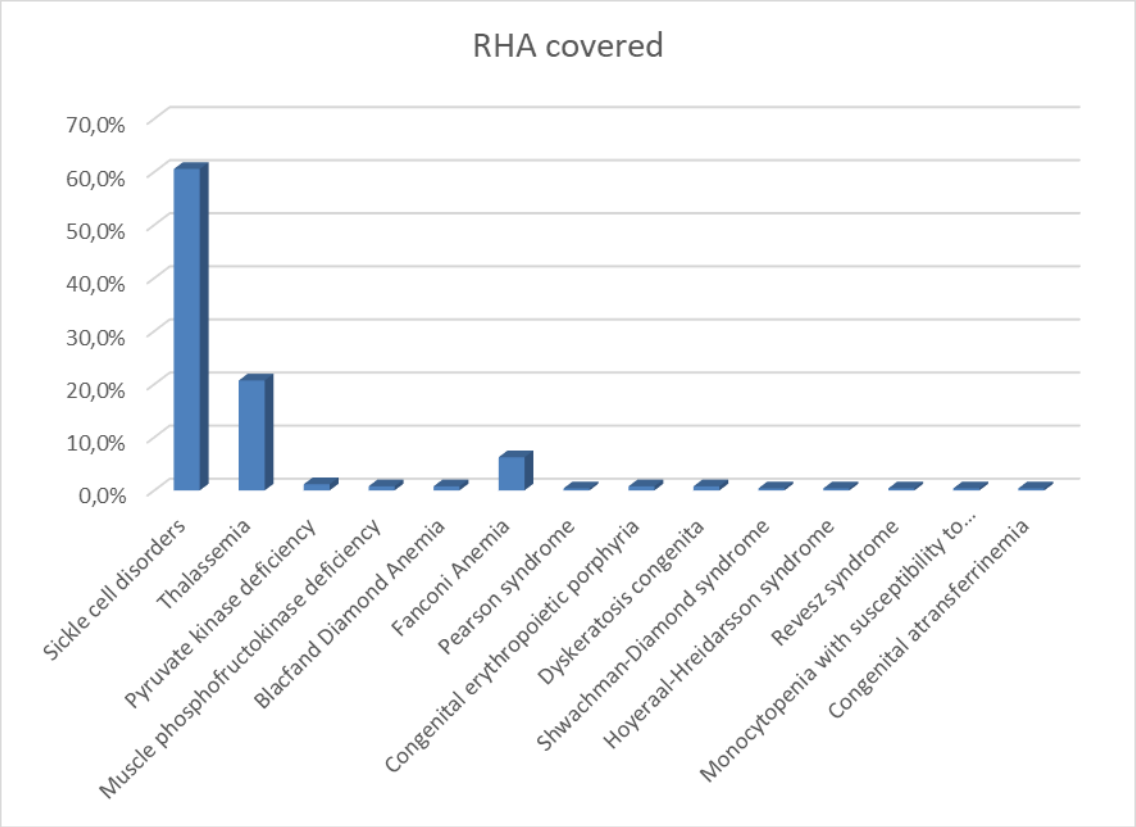


Fig. 11 CTs in % by RHA

As a result from the analysis, only 26 RHA from the 105 disorders classified as RHA (25%) are currently covered by at least one CT. This means that for 3 out of 4 very rare RHA have no CT is available, thus no new therapeutic option. RHA not covered by any CTs include in particular:

a) Chronic hemolytic anemias due to membrane disorders or channelopathies, as Hereditary Spherocytosis, Hereditary Ellyptocytosis, and Overhydrated / Dehydrated hereditary stomatocytosis

b) Constitutional dyserythropoietic anemias

c) Hemolytic anemias due to a enzymatic deficiency

d) Constitutional sideroblastic anemias

e) Constitutional anemia due to iron metabolism disorder

In addition, only 19% of the CTs are open in Europe and from this, only around the 50% are active in ERN-EuroBloodNet members from only 5 member states.

5.2.2 ERN-EuroBloodNet sponsoring Clinical Trials (CTs)

Based on the results from the analysis of the state of the art on CTs, ERN-EuroBloodNet has therefore started to conduct academic CTs in very rare diseases in which pharmaceutical companies have not planned CT. This includes:

- Luspatercept (an inhibitor of the transforming growth factor beta (TGF-β) superfamily) in Congenital Dyserythropoietic Anemia type II (CDAII) and congenital sideroblastic anemias, diseases requiring require regular red blood cell transfusions. Luspatercept, in those disorders, should be able to induce differentiation of erythroid cells, improve ineffective erythropoiesis, correct anemia and limit iron overload. Trial

principal investigators will be A Iolascon (Italy) and O Hermine (France), both centers being active HCP in EuroBloodNet

- Senicapoc in dehydrated hereditary stomatocytosis (DHS), also known as hereditary xerocytosis, a ultra-rare hemolytic anemia characterized by a decreased red cell osmotic fragility due to a defect in cation permeability, resulting in red cell dehydration and compensated hemolysis of different degrees. No treatment is available for this condition. Senicapoc (also known as ICA-17043) is a potent blocker of the Gardos channel, a calcium-activated potassium channel of intermediate conductance, in the red blood cell. Preclinical studies and studies in transgenic models of SCD show that inhibition of potassium efflux through the Gardos channel is associated with an increased hemoglobin level, decreased dense cells and decreased hemolysis. (principal investigator L Garçon).

Deliverable 7.1 Report on state of the art of Clinical Trials in Rare Hematological Diseases describe the methodology defined for the promotion of clinical research on RHAs in the frame of ERN- EuroBloodNet.

1.3. Project Results and Visibility

- Major results and key findings, their uptake and future potential use

The major results of second year of ERN-EuroBloodNet are:

The European inventory of RHD experts and facilities available at the EU and Member State levels based on the implementation of members, healthcare providers, departments and experts profiles have been updated based on:

a) new design of the interface for the Profiles' applications forms that will be available soon,

b) revision of the ORPHA classification for Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis subnetwork aiming to cover the existing gap for their correct classification.

A disease search tool has been implemented for the search of experts either by disease or by subnetwork with the possibility of include additional filters. The tool searches experts on the disease/subnetwork selected, not the disease/subnetwork the healthcare providers deal with.

The inventory is in continuous expansion, currently 166 experts have fulfilled completely their profiles, representing 70 more than previous year, and 225 departments, 5 more than last year. In parallel, in an effort to ensure the involvement of experts from the multidisciplinary teams, beyond the members representatives, in the activities implemented by the network, ERN-EuroBloodNet is identifying contact points in the specific sub thematic areas for each member. At this stage a total of 85 subnetworks representatives have been identified for 46 of the members.

This mapping exercise will be step-wise upgraded including indicators to continuously assess the excellence of the members, identify both the needs and the opportunities for a better allocation of resources, establishment of cross border agreements and promotion of networking for better delivery of care and engagement of clinical research. Special efforts will be made in the coming phases to expand geographical coverage especially involving Eastern countries.

The state of the art of Next generation sequencing (NGS) and Bone marrow transplantation (BMT) on non-oncological disorders has been analysed as highly specialized procedures key for the diagnosis or treatment of many non-

oncological RHD and presenting high inequalities for its access among MS. Two questionnaires were conducted among ERN-EuroBloodNet members with the gathering of 50 and 39 and responses received respectively. Answers allowed the identification of important gaps among the need and availability of a) NGS for rare anaemia disorders and b) BMT for Sickle cell disease.

Indicators linked to specific aspects of both highly specialized procedures will be defined and implemented in the members profiles for their monitoring and analysis of facilities available / needs at the national level.

Information on BMT will be complemented with the information gathered through the European Registry on Bone Marrow Transplant.

Opportunities for the establishment of cross border agreements on BMT for sickle cell disease have been analysed:

A Collaboration agreement for Crossborder Health for BMT on Sickle Cell Disease (SCD) pediatric patients has been established between two ERN-EuroBloodNet members, one from Italy (service provider) and one from Ireland (service receptor). It is worthy to mention that the collaboration agreement include the use of the Clinical Patient Management System (CPMS) for the sharing of clinical data of patients treated in the frame of the cross border agreement.

A second agreement is being initiated for BMT on SCD for adults between a member from France (service provider) and another from Belgium (service receptor).

European mapping of centres, number of patients and highly specialized procedures on Pyruvate Kinase Deficiency (PKD) has been performed given the identification of PKD as a very rare disorder that is under or misdiagnosed due to poor performance of enzyme activity assay although being a routine test. In addition, the **External Quality Assessment (EQAs)** for PKD is under development in a collaboration between ERN-EuroBloodNet and the UK-External Quality Assessment Service. Currently, it is on pilot phase involving 9 laboratories from 4 countries.

The same exercise will be expanded to cover rare iron metabolism disorders.

The list of international guidelines and recommendations has been expanded and classified based on Quality Domains, allowing the gathering of a total of 117 guidelines/recommendations for the six subnetworks and its classification based on: Scope and purpose, patients' involvement and Rigour of development.

International guidelines and recommendations endorsed by ERN-EuroBloodNet will be publicly available through the website searchable by disease, topic, involvement of patients and quality of evidence and consensus approach. GAPs for development of new guidelines and adaptation of existing documents to clinical practice guidelines are being identified and first proposal has been addressed to EHA Working group for official collaboration in their development. ERN-EuroBloodNet coordinators for guidelines are also involved at the coordination level at EHA Working group ensuring synergies and cooperation.

In addition, **two recommendations have been endorsed by ERN-EuroBloodNet through peer-review publications**:

- Addressing the diagnostic gaps in pyruvate kinase deficiency: Consensus recommendations on the diagnosis of pyruvate kinase deficiency
- Newborn screening for sickle cell disease in Europe: recommendations from a Pan-European Consensus Conference

The assessment of guidelines awareness and implementation will be undertaken focusing on mandatory highly specialized procedures potentially conflictive for their extensive compliance. First step in the assessment process has been the identification of 4 selected disorders to assess related guidelines implementation from 3 different subnetworks, specifically concerning to:

- Sickle Cell Disease - Red blood cell subnetwork
- HFE- Haemochromatosis - Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis subnetwork
- Anemia due to genetic disorders of iron metabolism and heam disorders - Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis subnetwork
- Myelodysplastic syndromes - myeloid malignancies subnetwork

In addition, the assessment of the "Addressing the diagnostic gaps in pyruvate kinase deficiency: Consensus recommendations on the diagnosis of pyruvate kinase deficiency" is being performed in parallel action with the European mapping of centers, patients and diagnosis on PKD.

Assessment of implementation of guidelines and recommendations through specific indicators will provide the basis for producing policy reports on existing inequalities on the clinical care of RHD patients although the existence of well-known and accepted international guidelines. The assessment will include the identification of the main barriers in order to facilitate their removal for a real implementation of guidelines.

Repository of education materials available for RHD has been created through the conduction of a questionnaire among ERN-EuroBloodNet members that has allowed a) the compilation of 152 educational material b) identification of concrete gaps for the promotion of generation of educational material c) identification of particular needs on specific disorders to be tackled. In addition, a **questionnaire for the available educational material for SCD patients** has been defined to complement the one already conducted in order to create a European repository of SCD educational material, given the high inequalities identified on the information available on the disease across countries.

A clear GAP on education has been identified for ultra-rare RHD both oncological and non-oncological. An eLearning platform will be developed for covering this GAP, make freely available educational material already existing, and create new one.

The first release of ERN-EuroBloodNet eLearning platform will include four disease specific modules with 3 main sections: a) Repository of documents, b) Repository of videos and c) Webinars . A dedicated section at the ERN-EuroBloodNet website will be created for the endorsement of the e-Learning platform. Contents will be publicly available.

The selection of the tools for the implementation of the e-Learning platform is based on the available tools provided by the DG SANTE's Information Systems Unit and in the context of the ERNs Working Group on IT Advisory Group and the WG on Knowledge Generation.

According to the ERN-EuroBloodNet educational aims, the most ideal platform to be implemented is a blended e-Learning platform using the combination of a Content management system (CMS) and a Learning management system (LMS).

After the fruitful demonstration by the EC of DEVCO Academy, https://webgate.ec.europa.eu/devco-academy/, Moodle tool for CMS and Webex meeting for LMS represents the perfect solution for ERN-EuroBloodNet eLearning platform.

In addition, a **Webinars program for health professionals** has been defined to provide cutting-edge knowledge on very rare diseases and highly specialised

procedures, avoiding the general speech around a rare disease, but focussing on a very innovative and specific disease, clinic or intervention area. A first list of 16 webinars and potential speakers has been identified. As mentioned above the system will be Webex meeting as it is freely available through the support of the EC, we have successfully experienced the system with the implementation of different online meetings of the network, sessions can be recorded in order to be publicly uploaded afterwards.

ERN-EuroBloodNet ePAGs collaborated in the organization of the "EHA Capacity Building Meeting" at the 23rd EHA congress in Stockholm from June 14-17, 2018 aiming to reinforce the sessions dedicated to patients celebrated within the EHA congresses. Collaboration is ongoing for the upcoming 24th EHA congress next June 13-16, 2019, in Amsterdam.

Definition of the programme for short stays for health professionals on Paroxysmal nocturnal hemoglobinuria (PNH) and Aplastic Anemia (AA), including highly specialized centers hosting the fellowships, agendas, teachers and focussed topics to be covered by each center. The call for participants will be open in the coming period of network implementation. Based also on the questionnaire for educational needs, further areas of expertise have been identified for potential organization of short stays for health professionals.

In addition, efforts will be focussed on the preparation of ERN-EuroBloodNet endorsed proposals for the EC programme Marie Skłodowska-Curie Actions (MSCA) in order to promote the European cooperation on training of young fellowships specially for haematological areas in which expertise is scarce and result less attractive for young clinicians and researchers.

The use and awareness of CPMS has been promoted among members. As a result, 12 panels have been opened for RHDs since the launch of the CPMS and the number of haematological experts who have a CPMS account increased from 12 (March 2018) to 55 (February 2019).

In addition, concrete projects are under discussion/have been launched for promotion of the use the CPMS in the following scenarios:

- Cross border agreement between Italy and Ireland for bone marrow transplantation on SCD patients paediatrics
- Virtual network for diagnosis and clinical care of cutaneous lymphoma
- Virtual network for diagnosis and clinical care of rare iron metabolism disorders

An upgrade of the CPMS "Preferences" section has been performed according to RHD specific needs. A proposal has already been submitted to the EC including a) the redefinition of the disease categories for each subnetwork based on ORPHA classification for grouping RHD b) proposal for inclusion of a new category for Bone marrow transplantation for both oncological and non-oncological disorders as a highly specialized procedure that may require virtual consultation.

The state of the art of the on-going clinical trials for rare hereditary anaemias (RHA) has been performed based on a desk research conducted on ClinicalTrials.gov website. A total of 256 CTs resulted from the analysis of the 105 disorders classified as RHA. From the analysis, only 26 RHA (25%) are currently covered by at least one CT. In addition, only 19% of the CTs are open in Europe and from this, only around the 50% are active in ERN-EuroBloodNet members from only 5 member states.

ERN-EuroBloodNet is sponsoring the use of innovative drugs in clinical trials. Those trials can be activated simultaneously in several member states through a EU directive on clinical trials allowing one country to be "main sponsor" and a few other countries to be "delegate sponsors". Proposals so far:

- Luspatercept in 2 Congenital Dyserythropoietic anaemia and other rare inherited anaemias
- Deoxygenated Red blood cell disorders: Sickle cell disease and Refractory sideroblastic anemia

A European Network of SCD Patients Organizations is being established in the frame of ERN-EuroBloodNet. The network will represent the umbrella of SCD National Patients Organizations in Europe, which will be authonomous and managed by members and national patients' representatives. Each country will have 2 spokesmen. One representative will be trained to become an ePAG for ERN-EuroBloodNet for SCD.

- Target groups and added value

The following targets are directly linked to the activities performed in the second year of ERN-EuroBloodNet, the added value for each target group is also included:

a) Expansion and update of member profiles in ERN-EuroBloodNet, including diseases covered
- o Healthcare professionals non-experts in RHD e.g. general practitioners, primary care paediatricians), searching for expert centres for patient referral.
- o Patients suffering from an RHD needed/requesting second opinion.
- o National health authorities requiring an evidence for the shaping of polices and better allocation of resources.

b) Analysis of the existing regulations impacting cross-border health and assessment of the impact of their implementation for RHD needs.
- o Healthcare professionals both experts and non-experts in RHD requiring to referral patients or samples to another MS for best delivery of care.
- o Patients suffering from an RHD requiring to be treated (or diagnosed) in a different MS.
- o Patient associations, especially at the national level, willing to inform patients about rights regarding cross border health.
- o National health authorities requiring evidence for the establishment of cross border referral agreements where needed

c) Creation of the repository of reliable guidelines and recommendations and their classification based on quality domains
- o National societies in charge of producing national guidelines and/or implementing European/International ones.
- o Healthcare professionals who are not experts in RHD in need of guidance
- o National policy makers to address the implementation of guidelines

d) Creation of the repository of educational material for health professionals and patients, implementation of Webinars program for health professionals and collaborate with ePAGs for "EHA capacity building" at EHA congress
- o Healthcare professionals who are not experts, willing to improve their skills for the care of patients with RHDs
- o Patients and patient associations willing to be involved in educational events organisation or increasing their knowledge about the disease

e) Provide inter-professional consultation by sharing of expertise and safe exchange of clinical information through the Clinical Patients Management System
- o Healthcare professionals within or out of ERN-EuroBloodNet who are not experts in RHDs seeking additional advice for complex cases.

f) Foster European cooperation in highly specialised procedures for diagnosis, innovative treatments and research
- o Health professionals, scientific societies and/or national authorities in charge of the maintenance of registries, willing to collaborate with RADeep for epidemiological surveillance of rare anaemias.
- o ERN-Eurobloodnet members willing to participate in the EJP on RDs project.

- European research infrastructures consortium e.g. ECRIN or other research groups within the IRDiRC for collaborative initiatives involving –Omics platforms, biobanking or other transversal platform supporting RD research
- Biotechnology and/or Pharma industry representatives willing to promote clinical trials and innovative research in orphan drugs.
- Bridges with other approved ERNs (eg ERN-RITA, PaedCan-ERN, TRANSCHILD…) will be strengthen when existing or new ones will be established in order to: a) ensure hematological RDs coverage, b) share common highly specialized procedures and c) ensure transition from childhood to adulthood.

g) Transversal activities undertaken in the frame of the ERNs Working Groups

- A common profit will benefit all ERNs by joining efforts in those aspects where a transversal action across all ERNs are needed, avoiding duplication of efforts and boosting the outcomes for a shared benefit.

- Further use of the project results

European inventory of RHD experts and facilities available at the EU and Member State levels

The upgrade on the ERN-EuroBloodNet profiles application forms will facilitate the completion of the information gathered through the profiles. The new interface will not only facilitate the selection of diseases from the ORPHA classification, but also will become more attractive to the experts fulfilling the profiles.

The revision of the ORPHA classification Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis subnetwork offers the opportunity to review the classification and suggest the proper adaptation to Orphanet, filling the current gap of the presence of these disorders on the ORPHA classification while enhancing their visibility and consideration.

The disease search engine will exploit the information in the inventory by facilitating the findability by health professionals or patients, of experts for concrete disorders and with special focus on different parameters, as area of expertise, patients' coverage, or country.

As general outcome, the European mapping of services will arise existing gaps in a certain MS or even at the EU level for the clinical management of a specific condition, allowing the better allocation of resources while setting the basis for the model for cross border referral system for patients and samples.

Also, by putting at disposition of health professionals and patients the expertise available for certain disorders will allow the establishment of new bridges for collaboration among experts and non-experts while facilitating the search for highly specialized knowledge and services for both health professionals and patients. The definition of new channels of communication among patients and experts will be deeper analyzed in order to facilitate this contact.

On the other hand, the European mapping of experts and services will make visible the lack of expertise for a given condition or procedure at the member, MS or EU level, information which will be valuable to identify gaps in education, and thus, to adapt the educational plan accordingly in the WP5 - TFA 3 Continuing Medical Education.

Another expected use from the implementation of members' profiles is the monitoring of excellence of the members. The services provided and specific diseases covered by each member will offer a complementary approach to the gathering of indicators for the regular monitoring of excellence of the members.

In this context, future actions for the upgrade and exploitation of the inventory are:

a) Upgrade of members profiles: members profiles will include the gathering of indicators to 1) map the “key” disease-specific criteria for the management of RHD patients and 2) monitor the excellence of the ERN-EuroBloodNet members. In result, the data already gathered through the inventory of ERN-EuroBloodNet members will not only be exploited but expanded while providing the evidence needed for the establishment of cross-border health pathways in the coming years of the network.

b) Automatic reports of activity: The implementation of a tool for automatic reports of activity on the centers performing specific highly specialized procedures is also foreseen in order to be spread to all the community, including peripheral centers for the identification of expert centers. Reports will be produced focused on specific diseases (instead of subnetworks) at the European and national level. Based on the information gathered in the inventory, automatic reports will be produced for the main medical conditions based on their prevalence, severity, and/ or particular medical management aiming to identify the existing gaps on number of experts, centers of expertise and services provided for a given disease/group of diseases while providing comparative data for the tackle of these conditions.

The state of the art of Next generation sequencing (NGS) and Bone marrow transplantation (BMT) on non-oncological disorders

Surveys were launched on 19th December 2018 and results were gathered until 10th January 2019. Accordingly, the Deliverable 3.2 and this report present preliminary results based on a first analysis of answers and number of responders. A second wave of results is expected including additional answers.

Information gathered will provide the evidence required for facilitating shaping public health policies addressing disease specific needs in the diagnosis and/or clinical management of the patient at the national level while shedding light into the current EU status of highly specialized procedures identified of added value for the establishment of a cross-border referral system.

Moreover, individual results will be compiled in internal document to be shared between members/responders in order to assess potential cross border agreements between medical centres for specific diseases.

Collaboration agreement for Crossborder Health for BMT on Sickle Cell Disease (SCD)

The establishment of the collaboration for Crossborder Health among Italy and Ireland has shown key hot points for its implementation, including the clinical protocol, administrative burden, legal framework and logistics and specially reimbursement scheme. A practical toolbox will be developed based on concrete needs and real cases of CBH for BMT in non-oncological RHD in order to:

a) facilitate the establishment of future agreements for CBH on highly specialized procedures
b) provide the evidence required as the base for discussion by the MS to enhance the political implication in the field.

European mapping of centres, number of patients and highly specialized procedures on Pyruvate Kinase Deficiency (PKD), establishment of External Quality Assessment (EQAs) and Recommendations on the diagnosis for PKD

Diagnosis of Pyruvate Kinase deficiency (PKD) has been identified as a routine test, but not available across Europe, representing an example of a chronic RHD in which diagnosis can be delayed for years, can be misdiagnosis or even been labelled as haemolytic anaemia of unknown origin forever due to:

- Lack of knowledge of the disease

- Heterogeneous clinical phenotype

- Technical problems: Recent transfusions, WBCs/platelet contamination, increased reticulocyte number, variants displaying in vitro normal enzyme activity

The identification of centers performing PKD diagnosis and facilities will contribute to a better understanding on the current status of PKD in European countries allowing the facilitation of the access to PKD diagnosis services.

As much important as identifying the medical centres concentrating patients and offering PKD diagnosis facilities is the identification of the GAPs. PKD patients are likely to be undiagnosed and/or misdiagnosed, probably due to the lack of facilities or expertise in a given country. In some countries, most of them are likely to not being genotyped due to economical shortages in the national health systems.

The up-to-date repository of medical centres will enable general practitioners, pediatricians or even hematologists to find experts on the disease to ask for advice and/or request appropriate diagnosis. This will impact in both a reduction of the number of PKD patients non-diagnosed or misdiagnosed and an increase on the number of PKD patients with a genetic diagnosis.

On the other hand, experts on PKD will be able to find colleagues especially in eastern countries to promote collaborative projects on research on PKD physio pathological mechanisms.

The PKD survey has been developed as an on-line application within the dedicated section of ERN-EuroBloodNet website allowing the publication of specific data through ERN-EuroBloodNet website to create the up-to-date inventory on medical centres and diagnosis facilities and the permanent access to the survey in order to update information from already listed centres or add new centres.

On the other hand, the foster of new EQAs for diagnosis of those RHDs needing for standardization of procedures across EU will have an impact on the number of cases underdiagnosed or misdiagnosed, allowing the provision of the correct treatment to the patient while contributing to a better epidemiological surveillance of the disease.

Altogether with the recommendation "Addressing the diagnostic gaps in pyruvate kinase deficiency: Consensus recommendations on the diagnosis of pyruvate kinase deficiency" that has recently being published by the American Journal of Hematology under the endorsement of ERN-EuroBloodNet, will help to other Centers and professionals to deliver timely and appropriate diagnosis and to increase awareness in PKD.

Future actions foreseen include:

- Exhaustive mapping diagnosis facilities for accurate PKD diagnosis and genetic characterization – Assessment of the implementation of Recommendations on PKD diagnosis: A second survey is being designed for the gathering of more exhaustive data on how expert centers perform PK diagnosis. The survey is being produced based on key indicators extracted from the “Consensus recommendations on the diagnosis of pyruvate kinase deficiency” that may not be widely implemented in the centers performing diagnosis and in collaboration with UKNEQAS.
- The EQAs for PK assay will be finalized following the participation of laboratories in the second phase foreseen for Q1 2019.
- Implementation of this methodology for other disorders as CDA and sideroblastic anaemia will be analysed.

List of international guidelines and recommendations and classification based on Quality Domains

The strategy followed for the creation of the repository of reliable guidelines and recommendations has led to the identification of the most common used

guidelines/recommendations at EU level for the most frequent RHD and to their classification according to quality domains in line with the Appraisal of Guidelines, REsearch and Evaluation (AGREE).

The classification of guidelines and recommendations based on quality domains has not been intended to be an exhaustive analysis of quality but a first practical classification for further analysis of gaps. The exercise has shed light on the current coverage of clinical practice guidelines (CPGs) for the four of the subnetworks analysed while allowing the identification unbalances among the different scopes and purposes. In addition, a clear need of patients' involvement in the generation of CPGs have been revealed. The analysis of the classification attending the rigour of development has also provided very valuable information of the grade of evidence used for their creation, while allowing the identification of areas where additional efforts are needed to increase the CPGs available as level A.

In this context, the next step is the finalization of the classification for the Bleeding and coagulation disorders and Lymphoid malignancies. Once the classification of CPGs on quality domains is completed, the action will allow the generation of the full picture of guidelines/recommendations available for RHD at EU level, and thus, the identification of areas covering all RHD needing for best practices promotion in collaboration with the European Hematology Association (EHA).

In addition, the repository will be publicly available on ERN-EuroBloodNet website allowing both non-experts and experts in RHD to benefit from an exhaustive database with reliable and updated guidelines. This will promote the delivery of highly specialised procedures and treatments and the harmonisation of care delivery across EU.

A deeper patients' involvement will be also promoted in next steps as cornerstone for guaranteeing their voice is heard in both, guidelines development and implementation based on their personal experience. ePAGs will also contribute to define priorities in guidelines production and/or adaptation to different populations. Important efforts will be dedicated to promote the incorporation of more ePAGs in the network for those conditions without representation, which are also the most lacking of clinical guidelines and/or recommendations.

In addition, ERN-EuroBloodNet is one of the members of the "ERN Working Group on Knowledge Generation" and will work together with other ERNs with the common goal of producing unique guidelines at the EU level by the best experts in the field, following a concrete methodology and validated at the national level.

Assessment of the level of awareness and implementation of existing guidelines

The assessment of guidelines awareness and implementation will supply the evidence needed to identify the main causes hampering their transposition into practical level while allowing to centralize efforts for overcome them. eg. Recommendations to working group on education and promotion of their practical transposition among national authorities through the National Contact Points.

The next step includes to continue the gathering the indicators for the assessment of the holistic clinical management of RHD conditions including prevention, diagnostic tests, treatment and follow up: The exercise and discussion on the guidelines selected as well as indicators for the evaluation are still ongoing, accordingly the final list will be provided in the upcoming period of the network.

Repository of education materials available for RHD and Webinars program for health professionals

The conduction of the questionnaire among ERN-EuroBloodNet members has allowed the creation of the repository of educational material while allowing the identification of educational needs in order to be addressed in the coming annual work plan with

the cooperation of EHA and ESH. The possibility of expanding the survey to non-members in order to complement the results is currently being analysed.

In order to cope with some of the educational gaps already identified, topic specific recorded video sessions will be provided by experts in the field allowing health professionals to learn highly specialized knowledge without the need to travel and whenever they wish. In addition, topic focused webinars allow to tackle questions gathered from the audience in real time, providing the perfect environment to nourish from the most outstanding experts in the field.

Next steps include:

- Complement the results obtained for SCD with the dedicated questionnaire for patients
- Develop criteria for the classification of educational material based on Quality Domains
- Make the repository publicly available at ERN-EuroBloodNet website
- Deeper analyse the gaps identified and make proposals for the creation of new educational material and organization of targeted webinars for health professionals
- The list of final Webinars topics will be agreed and potential speakers will be officially invited for the in order to finalize the annual webinars program. Webinars are expected to start by September 2019.
- Implementation of ERN-EuroBloodNet e-Learning platform – Project funded by CEF Telecom grant – Connecting EuroBloodNet II (Oct 2019 – Mar 2021)

Short stays for health professionals on Paroxysmal nocturnal hemoglobinuria (PNH) and Aplastic Anemia (AA)

Perceptorships aim to discuss AA, PNH, and other related bone marrow failure syndromes and to provide applicants with the fundamental tools for a correct diagnostic and treatment approach to marrow failures, including AA and PNH in children, adolescents and adult patients.

Next steps include

- A call for participants will be established and candidates will be chosen by a jury according to curriculum vitae and cover.
- Replicate the model for the establishment of SCD short stays

Promotion and upgrade of the CPMS

ERN-EuroBloodNet have dedicated special efforts during its second year of implementation to a) Increase the number of users as basis for the smooth running of the cases and b) Adapt the categorization of RHDs in the Preferences area according to the RHD needs as the key step to select properly the contributors to the panel.

On this last point, the first analysis for the upgrade of RHD categories for the Preferences has provided important information on the needs from the experts' point of view and shed light to continue working on this area.

On the other hand, based on the first cases enrolled in the platform, ERN-EuroBloodNet has also identified the main technical issues that have difficulted the access of new users to the platform. Based on this, a plan will be defined in order to ease these steps. Some of the actions contemplated will be:

- Report the EC the technical difficulties found and propose improvements in the system

- Produce of a shorter guide and FAQ questions to facilitate the access and navigation through the CPMS
- Analyse the possibility of holding webinars for short group of ERN-EuroBloodNet users a) To explain how to create the account in “real time” b) How to start using the platform

The state of the art of the on-going clinical trials for rare hereditary anaemias

Results from the analysis demonstrate urgent need to improve the access to CTs of patients affected by RHA across EU. ERN-EuroBloodNet has therefore started to initiate clinical trials in this field, and is planning other actions:

1) We have started to conduct academic CTs in very rare diseases in which pharmaceutical companies have not planned CT. This includes Ie.

a) Luspatercept in Congenital Dyserythropoietic Anemia type II (CDAII) and congenital sideroblastic anemias, diseases requiring require regular red blood cell transfusions.

b) Senicapoc in dehydrated hereditary stomatocytosis (DHS), also known as hereditary xerocytosis, a ultra-rare hemolytic anemia

To conduct those trials, ERN-EuroBloodNet will recruit a clinical research manager to carry out trial promotion and data monitoring. ERN-EuroBloodNet will also cooperate closely with companies for drug storing and shipping, and for pharmacovigilance

2) ERN-EuroBloodNet is currently identifying CTs using highly innovative treatments whose availability is limited in some EU-MS due to budget restrictions, lack of diagnostic procedures or various infrastructures, etc… The purpose would be contribute to set up conditions for implementation of such CTs in those EU members and or specific centers.

3) ERN-EuroBloodNet is also identifying HCPs which are currently not ERN-EuroBloodNet members but are very active in CTs for RHA in order to invite them to join the ERN in the upcoming Call for new membership.

- Major problems and lessons learned

It is undeniable that one of the major challenges of a complex network as ERN-EuroBloodNet is the consolidation of channels of communication for ensuring the involvement of all key actors. In this frame, one of the major problems faced during this year of implementation has been the lack of response from some of the subnetworks and TFA coordinators given the high number of commitments that European experts have apart from their works. In an effort to smoothly coordinate the different actions of the network, a new strategic structure has been adopted.

During ERN-EuroBloodNet second year of implementation 15 concrete projects have been launched focused on the different Transversal Fields of Actions and rare hematological diseases areas where members are already actively involved. In this way, each project has several active coordinators, who can be TFA/Subnetworks coordinators or not, that are in charge of the specific actions to be undertaken under concrete ongoing project.

In addition, this new strategic structure facilitates the involvement of members on those projects particularly of their interest while providing them the possibility to suggest new projects they are willing to launch under the umbrella of the network.

In line with this approach, a total remodelation of the website will be undertaken for the adoption of this new project-based structure (see 1.5 Overview of the dissemination activities – weaknesses of the dissemination activities).

On the other hand, some problems have been faced with the website developers for the provision of the upgrades foreseen in the ERN-EuroBloodNet members profiles and website for this period. In this context remedial actions have been undertaken to diminish as much as possible the impact on the delivery of the results. Thus, a new company has been selected for the next period of implementation for the taking over of the pending actions to be deployed concerning the website and inventory areas.

- Future recommendations

Face to face meetings are very valuable and necessary but more frequent follow-up of activities is needed by coordination through phone and video conferences with involved members in order to ensure that activities are develop as planned.

Also, for the face to face meetings, we consider that more practical interaction between members is needed. For this reason, we will organize once per year a two-days meeting with the Board of the network including parallel sessions topic-focussed allowing deeply discussion on on-going projects and new potential ones.

Technological partners are completely required for developing solutions for cross border health (eg. Inventory of ERN-EuroBloodNet members that will contribute to the mapping of available experts and serviced across EU) in order to ensure interoperability. Companies in charge of developing these tools should have expertise in eHealth and not only have informatics background. It is better to involve them as part of the project and not just as providers of services.

- Dissemination activities during and after the project

WP2 - DISSEMINATION

Dissemination has been one of the ERN-EuroBloodNet key transversal activities, becoming a priority for the whole consortium in order to increase the outreach of the outcomes achieved.

ERN-EuroBloodNet's dissemination includes all the activities aiming to expand knowledge of the ERN in RHDs, its website and its activities and services in order to get the necessary critical mass to make the network fully successful and ensure its long-term sustainability.

Specific objectives for the second year of implementation of ERN-EuroBloodNet were:

a) to exploit and update the ERN-EuroBloodNet's website (www.eurobloodnet.eu) as the main tool for the dissemination of results and offering services and up-to-date information to patients and health professionals,

b) to promote the use of the ERN Collaborative Platform among the ERN-EuroBloodNet members for its consolidation as the official platform for sharing of documents and communication among members

c) to promote new collaboration agreements with third parties and strengthen the existing ones.

All dissemination activities undertaken in the WP of Dissemination are fully detailed in section 1.7 Description of the activities carried per WP

- Project website

WP2 - DISSEMINATION

Task 2: ERN-EuroBloodNet website

ERN-EuroBloodNet website has become the main tool of dissemination of the network since its release last July 2017, providing the skeleton of the complex structure that ERN-EuroBloodNet represents by endorsing specific dedicated sections to the all the activities and tools developed by the networks while ensuring interoperability with other platforms.

ERN-EuroBloodNet website has been conceived as the on-line platform that provides not only the door of access to ERN-EuroBloodNet dynamic and public inventory of members and experts but also to the main tools developed and implemented during the running time of the network.

In this context, ERN-EuroBloodNet website can be understood as two-side online platform with two main objectives:

- ERN-EuroBloodNet website as the main tool for dissemination of the goals and achievements to boost public awareness of the network.
- ERN-EuroBloodNet website as the infrastructure (web portal and database) for accessing the Inventory of ERN-EuroBloodNet members and experts profiles
- New sections and specific target-actions engines have been implemented in this period for the exploitation of the data collected while keeping the website in an evolving environment attending to the network's need.

The implementation of ERN-EuroBloodNet website is fully explained at section 1.7 Description of the activities carried per WP

1.4. Overview of the evaluation activities and results

- Participant or partner feedback

During the first year of implementation, ERN-Coordination team already realized that the participation of members in the network activities were very different according to subnetworks and/or countries.

In order to analyse the weak points on members participation in the different activities performed an output document was generated compiling attendance / participation of members in the different activities undertaken by the network.

Figure 12 shows the percentage of participation of the 66 members in the different activities monitored: attendance to BoN meetings answers to cross-border health questionnaires on Next generation sequencing and Bone marrow transplantation for non-oncological diseases (55 members belonging to the non-oncological hub have been contemplated for the % analysis), answers to the continuing medical education questionnaire, login in the CPMS and reporting of clinical trials on very rare or breakthrough drugs.

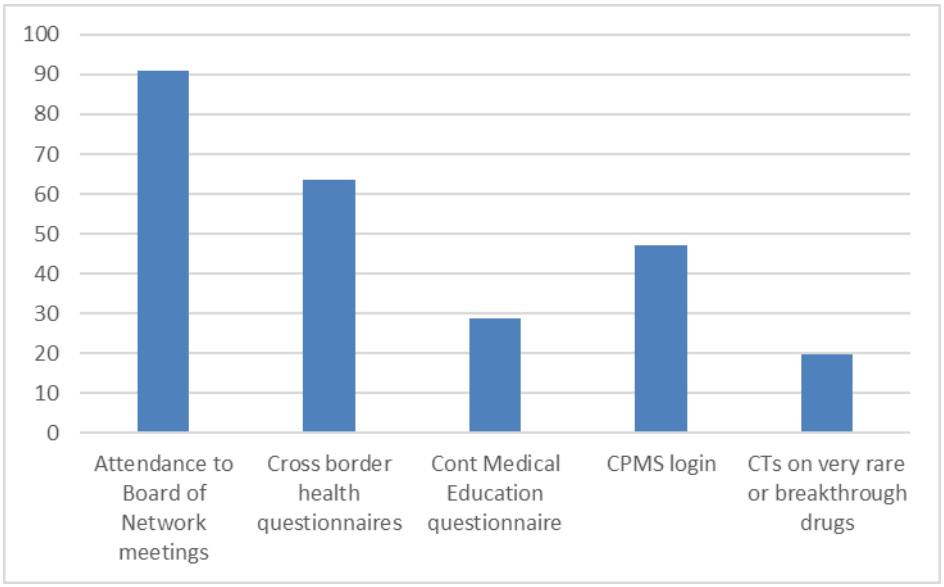


Fig. 12 Percentage of participation of members in different activities of the network

Regarding the attendance to ERN-EuroBloodNet Board of the Network (BoN) meetings, 12 members have not been represented either in the 1st or 2nd BoN meetings. However, representatives from 3 of these members are part of the Scientific and Strategic Board and have properly attended those meetings, and representatives from other 3 members have participated on complimentary face to face meetings, as the Kick off in Vilnius, or the informal meetings organized during EHA congress. Accordingly, 6 members (10%) have never attended a face to face meetings.

Taking into consideration the different actions monitored on answers to questionnaires, creation of CPMS accounts and contribution to the list of CTs, 17 members (25,76%) have not participated in either of the requested actions.

Figure 13 shows the percentage of level of response of the scientific and strategic board (SSB) members in the different concrete actions where their action was requested: participation in SSB meetings, contribution on the list of international guidelines and recommendations and identification of indicators for their assessment. For the calculation of the percentage, 33 members of the SSB have been contemplated for the analysis of the SSB meeting, while 17 members have been contemplated for the actions on guidelines and recommendations as contribution was only requested to subnetworks coordinators.

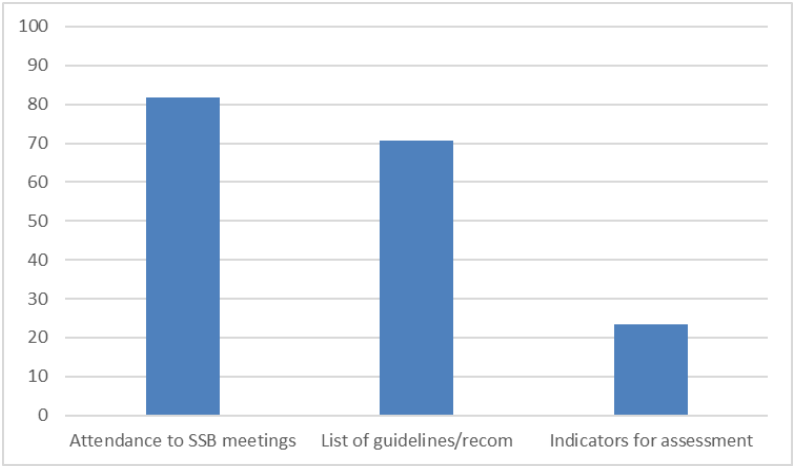


Fig. 13 Percentage of participation of SSB members in different concrete actions where their input was requested.

Analysing the participation of the SSB in the four meetings held so far, 6 members of the SSB have never participated (18,18%), 3 of them being part of the Independent Advisory Board.

BoN and SSB members showing low participation will be directly contacted by the coordination team to identify / understand which are the main barriers preventing them to increase their participation in the network activities. For this, a structured interview will be conducted by phone specifically addressing common barriers already identified (i.e. ERN activities are not considered as part of their daily activity).

In addition, during the first year of implementation, ERN-Coordination team directly gathered the feedback from partners by conducting a questionnaire of satisfaction on Communication and coordination of the work. A second wave of answers will be gathered during the third year.

- Process evaluation – Please use indicators specified in Annex 1 to the Grant Agreement)

Indicator 1		
Specific Objective	**Nature / Type of indicator**	**Linked task**
1-Improve equal access to highly specialized healthcare delivery for RHD across Europe.	Qualitative/ Process indicator	Task 1.1. Mapping of services (clinical and diagnosis) available in Europe for best clinical care
Definition	**Target Value**	**Value reached**
Upgraded version of the on-line inventory of: (i) experts, (ii) centres, and (iii) facilities available for RHD, especially for point (iii)	on-line application for updating members profiles (link provided) including facilities considered high specialized procedures.	Partially implemented - The complete upgrade of the ERN-EuroBloodNet inventory of members and experts will be implemented in the next period of network implementation due to difficulties experienced with website developers.
Indicator 2		
Specific Objective	**Nature / Type of indicator**	**Linked task**
1-Improve equal access to highly specialized healthcare delivery for RHD across Europe.	Qualitative/ Process indicator	Task 1.1. Mapping of services (clinical and diagnosis) available in Europe for best clinical care
Definition	**Target Value**	**Value reached**
Repository search engine	A search engine will be implemented allowing multiple type of queries to the repository based on ORPHA classification.	https://www.eurobloodnet.eu/search
Indicator 3		
Specific Objective	**Nature / Type of indicator**	**Linked task**
1-Improve equal access to highly specialized healthcare delivery for RHD across Europe.	Qualitative/ Process indicator	Task 1.1. Mapping of services (clinical and diagnosis) available in Europe for best clinical care
Definition	**Target Value**	**Value reached**
Mapping of diagnosis facilities for ultra rare RHDs	At least two new diseases will be covered ie. Dyserythropoietic anaemia and hereditary xerocytosis	Partially implemented – Agreements have been reached with members to cover to ultra-rare conditions: a) Rare iron metabolism and b) cutaneous lymphoma Questionnaires are under development and will be implemented on-line during the 3rd year (new company already identified for programming tasks)

Indicator 4		
Specific Objective	**Nature / Type of indicator**	**Linked task**
2-Promote the best practices in prevention, diagnosis and safe clinical care across Europe	Qualitative/ Process indicator	Task 2.1. Create a comprehensive public database of reliable guidelines
Definition	**Target Value**	**Value reached**
Repository of existing guidelines / recommendations	On-line repository on guidelines accessible through ERN-EuroBloodNet website	Partially implemented - Repository of guidelines and recommendations has been created. It will be open available in the website in the next period if network implementation. (new company already identified for programming tasks)
Indicator 5		
Specific Objective	**Nature / Type of indicator**	**Linked task**
3-Disseminate cutting-edge knowledge and facilitate the continuous medical education in the field of RHD	Qualitative/ Process indicator	Task 3.1. Identification of educational GAPs survey in collaboration with EHA
Definition	**Target Value**	**Value reached**
Methodology to identify educational GAPs	Consensus agreement based on cons and pros of the 3 approaches presented to identify educational GAPs	Deliverable 5.1 - Report on educational GAPs
Indicator 6		
Specific Objective	**Nature / Type of indicator**	**Linked task**
3-Disseminate cutting-edge knowledge and facilitate the continuous medical education in the field of RHD	Qualitative/ Process indicator	Task 3.3. Co-organization with the ePAGs of European symposia with interactive patient participation
Definition	**Target Value**	**Value reached**
Planning of the Symposium with patients	Agreement on topics, speakers and management of the organization of the symposium with the EHA	"EHA Capacity Building" within the 23 rd EHA congress in Stockholm from June 14-17, 2018.
Indicator 7		
Specific Objective	**Nature / Type of indicator**	**Linked task**
4-Provide inter-professional consultation by sharing of expertise and safe exchange of clinical information	Quantitative/ Process indicator	Task 4.1. Pilot testing of the CPMS
Definition	**Target Value**	**Value reached**
Pilot testing of CPMS	Minimal number of cases entered into CPMS for pilot testing: 5	6 patients entered in the pilot phase
Indicator 8		
Specific Objective	**Nature / Type of indicator**	**Linked task**
5-Foster European cooperation in highly specialized procedures for diagnosis, innovative treatments and research	Quantitative/ Process indicator	Foster European cooperation in highly specialized procedures for diagnosis, innovative treatments and research
Definition	**Target Value**	**Value reached**
Establishment of a committee to assess research funding opportunities	At least 4 members involved in the committee	Delayed - This task has been delayed since other concrete projects have been identified as priorities by the scientific and strategic board. However, the activity will be retaken in the 3rd year including the training of one coordination staff member on professional software for grants

		research

Indicator 9		
Specific Objective	**Nature / Type of indicator**	**Linked task**
5-Foster European cooperation in highly specialized procedures for diagnosis, innovative treatments and research	Qualitative/ Process indicator	Task 5.2. To promote the participation in clinical trials
Definition	**Target Value**	**Value reached**
State of the art of CTs in RHD	Report on State of the art of CTs in RHD	Deliverable 7.1 - Report on state of the art of CTs in RHD

- Output evaluation – Please use indicators specified in Annex 1 to the Grant Agreement)

Indicator 10		
Specific Objective	**Nature / Type of indicator**	**Linked task**
1-Improve equal access to highly specialized healthcare delivery for RHD across Europe.	Quantitative/ Output indicator	Task 1.1. Mapping of services (clinical and diagnosis) available in Europe for best clinical care
Definition	**Target Value**	**Value reached**
Number of members' profiles created	200. Members profiles involved in the multidisciplinary team created in the on-line inventory within EuroBloodNet website.	267 experts have already created their profiles in the ERN-EuroBloodNet directory, including both members representatives and substitutes and experts invited by them. 166 of them have fulfilled completely their profiles.
Indicator 11		
Specific Objective	**Nature / Type of indicator**	**Linked task**
2-Promote the best practices in prevention, diagnosis and safe clinical care across Europe	Quantitative/ Output indicator	Task 2.1. Create a comprehensive public database of reliable guidelines
Definition	**Target Value**	**Value reached**
Repository of existing guidelines / recommendations	At least 100 guidelines / recommendations identified for RHD	117 guidelines and recommendations have been compiled
Indicator 12		
Specific Objective	**Nature / Type of indicator**	**Linked task**
2-Promote the best practices in prevention, diagnosis and safe clinical care across Europe	Quantitative/ Output indicator	Task 2.3. Foster the creation of new guidelines in collaboration with EHA and their transposition at the national level
Definition	**Target Value**	**Value reached**
Foster the creation of new guidelines	Based on gaps identified, identification of at least one guideline to be promoted per sub-thematic area	Concrete areas where creation of guidelines and recommendations can be promoted are included in Deliverable 4.1 Report on the comprehensive public database of reliable guidelines
Indicator 13		
Specific Objective	**Nature / Type of indicator**	**Linked task**

3-Disseminate cutting-edge knowledge and facilitate the continuous medical education in the field of RHD	Qualitative/ Output indicator	Task 3.1. Identification of educational GAPs survey in collaboration with EHA
Definition	**Target Value**	**Value reached**
Actions taken to identify educational GAPs	Report on the actions taken in order to identify educational GAPs and plan how to address them	Deliverable 5.1 - Report on educational GAPs
Indicator 14		
Specific Objective	**Nature / Type of indicator**	**Linked task**
3-Disseminate cutting-edge knowledge and facilitate the continuous medical education in the field of RHD	Qualitative/ Output indicator	Task 3.1. Identification of educational GAPs survey in collaboration with EHA
Definition	**Target Value**	**Value reached**
Celebration of the Symposium with patients	Symposium celebrated within the 23 rd EHA congress in Stockholm from June 14-17, 2018.	"EHA Capacity Building" within the 23 rd EHA congress in Stockholm from June 14-17, 2018.
Indicator 15		
Specific Objective	**Nature / Type of indicator**	**Linked task**
4-Provide inter-professional consultation by sharing of expertise and safe exchange of clinical information	Qualitative/ Output indicator	Task 4.1. Pilot testing of the CPMS
Definition	**Target Value**	**Value reached**
Report on feedback from the CPMS pilot phase experience	Feedback from members on pilot testing and needs for RHD complex cases	Feedback on the CPMS pilot exercise reported to the EC in March 208
Indicator 16		
Specific Objective	**Nature / Type of indicator**	**Linked task**
5-Foster European cooperation in highly specialized procedures for diagnosis, innovative treatments and research	Qualitative/ Output indicator	Foster European cooperation in highly specialized procedures for diagnosis, innovative treatments and research
Definition	**Target Value**	**Value reached**
List of the research funding opportunities	Up-to-date list with the open calls and research funding opportunities for RHD	Delayed - This task has been delayed since other concrete projects have been identified as priorities by the scientific and strategic board. However, the activity will be retaken in the 3rd year including the training of one coordination staff member on professional software for grants research
Indicator 17		
Specific Objective	**Nature / Type of indicator**	**Linked task**
5-Foster European cooperation in highly specialized procedures for diagnosis, innovative treatments and research	Quantitative/ Output indicator	Task 5.2. To promote the participation in clinical trials
Definition	**Target Value**	**Value reached**

State of the art of CTs and drug availability in RHD	Identification of at least 2 sub thematic areas/diseases where cooperation with pharma is particularly required due to the lack of CTs / treatments	Sub thematic areas/diseases where cooperation with pharma is particularly required due to the lack of CTs are included in Deliverable 7.1 - Report on state of the art of CTs in RHD

- Outcome evaluation – Please use indicators specified in Annex 1 to the Grant Agreement)

Indicator 18		
Specific Objective	**Nature / Type of indicator**	**Linked task**
1-Improve equal access to highly specialized healthcare delivery for RHD across Europe.	Quantitative/ Outcome indicator	Task 1.1. Mapping of services (clinical and diagnosis) available in Europe for best clinical care
Definition	**Target Value**	**Value reached**
Usefulness of website	70% of satisfaction among users on the website services assessed through a survey	Delayed - Survey not conducted due to the technical problems faced
Indicator 19		
Specific Objective	**Nature / Type of indicator**	**Linked task**
2-Promote the best practices in prevention, diagnosis and safe clinical care across Europe	Quantitative/ Outcome indicator	Task 2.1. Create a comprehensive public database of reliable guidelines
Definition	**Target Value**	**Value reached**
Dissemination of awareness of the repository among target audiences	Collaboration established with at least 10 national scientific/educational associations to disseminate the repository among their members. i.e. websites' cross links	Delayed - Dissemination of the repository will be performed once it is public available at the ERN-EuroBloodNet website. (new company already identified for programming tasks)
Indicator 20		
Specific Objective	**Nature / Type of indicator**	**Linked task**
3-Disseminate cutting-edge knowledge and facilitate the continuous medical education in the field of RHD	Quantitative/ Outcome indicator	Task 3.3. Co-organization with the ePAGs of European symposia with interactive patient participation
Definition	**Target Value**	**Value reached**
Number of patients attending the symposium	Target value: 35	69 attendants to the EHA capacity building at the EHA congress 2018
Indicator 21		
Specific Objective	**Nature / Type of indicator**	**Linked task**
4-Provide inter-professional consultation by sharing of expertise and safe exchange of clinical information	Quantitative/ Outcome indicator	Task4.3. Promote CPMS use among members
Definition	**Target Value**	**Value reached**
Number of cases entered in CPMS for advice	Minimal number of cases entered into CPMS for advice: 10	12 cases have been entered into the CPMS

Indicator 22		
Specific Objective	**Nature / Type of indicator**	**Linked task**
4-Provide inter-professional consultation by sharing of expertise and safe exchange of clinical information	Quantitative/ output indicator	Task4.3. Promote CPMS use among members
Definition	**Target Value**	**Value reached**
Number of users of the CPMS	Minimal number of users of the CPMS: 20	55 experts have registered in the CPMS
Indicator 23		
Specific Objective	**Nature / Type of indicator**	**Linked task**
5-Foster European cooperation in highly specialized procedures for diagnosis, innovative treatments and research	Quantitative/ output indicator	Task 5.3. To facilitate the provision of –omics platforms and new technologies
Definition	**Target Value**	**Value reached**
Collaborative research projects	At least one proposal of collaborative research project within EuroBloodNet umbrella.	A joint proposal under the umbrella of the network was submitted to the EJP on RD call "Transnational research projects to accelerate diagnosis and/or explore disease progression and mechanisms of rare diseases" - IDEA, Innovative Diagnostic Evaluation of rare Anaemias
Indicator 24		
Specific Objective	**Nature / Type of indicator**	**Linked task**
5-Foster European cooperation in highly specialized procedures for diagnosis, innovative treatments and research	Quantitative/ output indicator	Task 5.1. To facilitate European epidemiological surveillance of RHD
Definition	**Target Value**	**Value reached**
Registries participating with RADeep	At least 2 national registries participating in the pilot phase of RADeep	Agreements have been reached for the participation in RADeep of: - Spanish registry for SCD and Thalassaemia patients - French registry for thalassaemia patients - French registry for pyruvate kinase deficiency patients - German registry for SCD patients

In general, all the target values have been reached during second year of implementation. Some of the indicators related to the website are delayed due to some technical problems faced for the upgrade of the ERN-EuroBloodNet inventory and website sections (see 1.9 Deviations from Annex 1). However remedial actions have already been taken for the minimization of the impact as much as possible.

1.5. Overview of the dissemination activities

- Please comment on the Strength of the dissemination activities

The design and implementation of a robust communication strategy and plan is cornerstone to creating a critical mass of interests necessary for the upgrading of services provided by the experts and expert centres included in ERN-EuroBloodNet, and to increase public awareness of RHD and of network goals and achievements.

The bidirectional communication of the network requires permanent contacts between the board of ERN-EuroBloodNet and different target groups including a) National and EU health authorities and policy makers b) Healthcare Providers, universities and research centres c) Scientific and national bodies at the national, EU level and international d) Patients' associations, patients and relatives.

Liaison with third parties outside Europe are also promoted since this will add value to the network by promoting the development and use of registries as well as disseminating information on RHD in neighbouring countries. Both EHA and EURORDIS have links outside of EU that will be informed regularly and invited to dialogue through the communication tools of ERN-EuroBloodNet. This provides a means to strengthen networking and international collaborations and ensure sustainability of the network.

ERN-EuroBloodNet Dissemination strategy was described in the Dissemination plan defined during the first year of the network aiming to set the basis for the overall strategy to promote and expand the knowledge of ERN-EuroBloodNet to the different stakeholders already identified for the five years of implementation, including five main objectives to be achieved:

- Objective 1: To define and establish a dissemination plan including creation of the dissemination material (ie Leaflets, slide presentations…) and creation of a Dynamic Stakeholders Directory
- Objective 2: To develop and stimulate ERN-EuroBloodNet social media channels as the main powerful tools for dissemination, including ERN-EuroBloodNet website, ERN Collaborative platform, newsletter and social networks.
- Objective 3: To promote collaboration agreements with third parties: other ERNs, European Research Infrastructures Consortiums.
- Objective 4: To increase awareness and knowledge on RHD through the organization of European Symposia for health professionals and patients.
- Objective 5: To disseminate reports on ERN-EuroBloodNet outcomes via website and ERN Collaborative platform to improve clinical care and increase public awareness, together with a final publication.

The specific tasks addressed to achieve the targets objectives have led to an excellent result on the dissemination activities (see 1.3 Project results and visibility - Dissemination activities during and after the project and 1.7 Description of the activities carried per WP).

- Please comment on the Weaknesses of the dissemination activities

During the second year of ERN-EuroBloodNet implementation, activities have been successfully addressed aiming to fulfil the specific objectives contemplated in the dissemination plan. For the prioritization of activities to be implemented during next period, feedback from ERN-EuroBloodNet SSB and members has been analysed in order to identify the more weaknesses and urgent actions to be undertaken in the dissemination field.

Accordingly, some of the needs identified and dedicated actions that will be undertaken in the coming period are:

Improvement on the dissemination at national level

A board of National Contact Points (NCPs) is currently being defined as key actors in the dissemination of ERN-EuroBloodNet activities and results at national level.

The board will follow the structure defined in the coordination of the subnetworks and TFAs including the designation of a contact person from the oncological hub, non-oncological hub and patient representative by MS.

NCPs will become the bridges among the network and national authorities and scientific societies ensuring that results obtained in the network create an impact at the national level. Their activity will become cornerstone in the following years of implementation if the network as concrete results potentially impacting the shaping of policies have been already obtained.

Expansion of ERN-EuroBloodNet website sections

ERN-EuroBloodNet website is defined by its dynamism not only in its content, but also in the evolution of its structure in the flexible way that a complex network as ERN-EuroBloodNet requires for covering its needs.

In this context, next steps foreseen are:

1. Repertory of existing patient associations across EU and Patient Associations profiles: In addition to the 11 pan-European umbrella organizations already identified and listed at the Patients' advocacy section, associations will be able to create their profiles through an easy-to-fill form, in a similar way to members' profiles.

2. Educational Material section: a dedicated section will be created including different educational material with the objective to get EU citizens, not only RD patients, aware of RHDs dimensions, values and burdens. For example it is foreseen to upload different webinars from the EHA Advocacy Sessions covering different topics: clinical trials and research, access to care and cure, patient awareness and empowerment, patients' rights.

3. Agenda section: An agenda section will be implemented in ERN-EuroBloodNet website fed from the events suggested by other websites and the relevant events suggested or organized by the ERN-EuroBloodNet members to collect information about national and international scientific congresses on RHDs, as well as symposia, workshops and other activities of interest for health professionals, patients and patients' associations

4. Implementation of directories created under the frame of specific Transversal field of actions, eg. Inventory of guidelines, existing registries on RHD...

5. Establishment of electronic links with third parties: specific section dedicated to visualize the collaborative efforts and the constant relation with other projects and initiatives.

ERN-EuroBloodNet website availability in other languages

All information provided in ERN-EuroBloodNet website are in English, becoming an obstacle if citizens, patients or helaht professionals search for information in their local language.

A possible solution is being analysed based on a multi-lingual and cross-lingual software, machine translation and knowledge based system, including queries and returning machine-translated pertinent excerpts. It would facilitate the dissemination of high quality RDs information creating a linguistic cross-border access to relevant knowledge of all aspects of RDs cure and care.

Improvement of dissemination of current actions undertaken by ERN-EuroBloodNet to members

In this area, the ERN-EuroBloodNet newsletter has been already designed in order to transmit directly to the members the most relevant RHD news and activities implemented by the network in real time and will be launched in the coming weeks together with the release of the dedicated section in the website.

Dissemination of ERN-EuroBloodNet knowledge among Member States Stakeholders, public authorities and health institutions

Annual ERN-EuroBloodNet reports produced across the five TFAs will be public accessible through website and ERN collaborative platform and spread to other ERNs and target groups depending on the nature of the report.

- (if applicable) Update of the plan for dissemination of results

The actions described in the previous section identified as a priority for for the third year of implementation does not imply a change in the dissemination plan since they were already addressed within the frame of the 5 years of ERN-EuroBloodNet.

1.6. Objectives

- List the specific objectives for the project and describe the activities carried out during the reporting period towards the achievement of each listed objective. Provide clear and measurable details.

In agreement with the Directive 2011/24/EU on the application of patients' rights in cross-border healthcare, ERN-EuroBloodNet established 5 specific objectives to be accomplished during the five years running time of the network. For the second year the following activities were carried out towards the achievement of each specific objective:

Specific Objective 1. Improve equal access to highly specialised healthcare delivery for RHD across Europe.

- To expand and update the European repository of ERN-EuroBloodNet experts and facilities.

ERN-EuroBloodNet inventory of members and experts was implemented during the first year of the network. Members profiles' edition is available through a set of applications forms that have been designed integrating the ORPHA classification for RHD.

In this period, an upgrade of the interface for the Profiles' applications forms has been designed while the ORPHA classification for Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis subnetwork is being reviewed aiming to cover the existing gap for their correct classification.

Also, a disease search tool has been implemented for the search of experts either by disease or by subnetwork with the possibility of include additional filters.

Currently, 166 experts have fulfilled completely their profiles, including 85 subnetworks representatives already identified for 46 of the members. Moreover, 225 departments profiles have been completed.

- To identify gaps in services available for best patient care and promote new actions to address them.

In agreement with the priorities identified in the RHD field for the establishment of cross-border agreements, two online surveys were conducted among ERN-EuroBloodNet members with focus on highly specialized procedures key for the diagnosis or treatment of many non-oncological RHD and presenting high inequalities for its access among MS: Bone marrow transplant and NGS for non-oncological disorders. A total of 39 and 50 responses were received respectively.

The first wave of answers has allowed the identification of important gaps among the needs and availability of these highly specialized procedures of added value for the

establishment of cross-border referral system. In this sense, a pilot project for cross border health between two ERN-EuroBloodNet members from Italy and Ireland has been established to allow access to BMT for Irish patients with Sickle Cell Disease.

In addition, Pyurvate Kinase enzyme assay for the diagnosis of Pyruvate Kinase Deficiency (PKD) was identified as a routine test commonly misinterpreted or lacking at the European level, leading to an underestimation of the real number of patients. The European mapping of centres, number of patients and highly specialized procedures on PKD has been performed gathering 41 medical centres from 10 countries. Based on the results, a total of 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 diagnosis per year.

- To analyse the existing regulations regarding cross-border health and assess the impact of their implementation for RHD needs.

A dedicated task force has already been established for the analysis of the Collaboration agreement for BMT on SCD among Italy and Ireland for the identification of the critical and most conflictive issues for its establishment, including the identification of the variables that can be adapted at the National level impacting on the establishment of CHB agreements according to the national regulations. As a result of the analysis, a CBH toolbox will be created to a) facilitate the establishment of future agreements for CBH on highly specialized procedures b) provide the evidence required as the base for discussion by the MS to enhance the political implication in the field.

Specific Objective 2. Promote best practice in prevention, diagnosis and clinical care across EU

- To expand the already initiated repository of comprehensive public database of reliable evidence-based guidelines

The list of international guidelines and recommendations created during first year of the network has been expanded with a total 117 documents for the six subnetworks, representing the most frequent guidelines and recommendations used for the main RHD conditions.

- To assess the guidelines already gathered through the repository by AGREE methodology.

Guidelines and recommendations were classified based on Quality Domains in line with domains in line with the Appraisal of Guidelines, REsearch and Evaluation (AGREE) and according to three domains: Scope and purpose, patients' involvement and Rigour of development.

A total of 24 guidelines/recommendations for RBC, 13 for BMF, 6 for HH-Iron and 26 for Myeloid were classified based on quality domains with the participation of 10 ERN-EuroBloodNet experts. The task is still ongoing for the Bleeding and coagulation disorders and Lymphoid malignancies.

- To assess the level of awareness and implementation of existing guidelines.

The first actions have been undertaken for the identification of a) concrete guidelines/recommendations addressing specific disorders expected to be poorly implemented in MS, and b) clinical outcome indicators having some pointing to the minimal requirements and/or related to highly specialized procedures.

The first round of answers gathered a total of 4 selected disorders to assess related guidelines implementation from 3 different subnetworks.

In addition, the assessment of the "Addressing the diagnostic gaps in pyruvate kinase deficiency: Consensus recommendations on the diagnosis of pyruvate kinase

deficiency" is being performed on two approaches: a) Mapping of centers performing PKD diagnosis and facilities for accurate diagnosis and genetic characterization (linked to Specific Objective 1) and b) Establishment of the External Quality Assessment on PK diagnosis in collaboration with UKNEQAS

Specific Objective 3. Disseminate cutting-edge knowledge and facilitate continuous medical education in the field of RHDs

- To identify the unmet educational needs, especially in the case of ultra RHDs.

The collaboration established wiht European Hematology Association (EHA) and European School of Hematology (ESH), has been strengthen in order to joint efforts towards the better identification of educational gaps and needs on RHD as the basis for the establishment of a work plan to address them.

A questionnaire was conducted among ERN-EuroBloodNet members in order to a) compile educational material for professionals or patients and b) identify and assess the educational needs within the network. A total of 21 answers compiling feedback from 27 experts were received from ERN-EuroBloodNet members belonging to 9 European Member States. A total of 152 educational materials were compiled and classified according the criteria assigned in the template, allowing the identification of areas where the creation of new material can be promoted.

ERN-EuroBloodNet has defined a Webinar program for health professionals aiming to cope with the educational gaps identified through the questionnaire while focussing on a very innovative and specific disease, clinic or intervention area. List of potential webinars has already been drafted, foreseen to be started in September 2019.

In addition, the gathering of the educational material for SCD patients available was identified as an urgent need since the awareness level of the disease and the presence of the patients organizations are extremely varied from country to country as a disorder linked to migration flows from African and Middle East countries. Accordingly, ERN-EuroBloodNet is currently identifying the SCD patients' needs across European Member States. A questionnaire has already been defined for collecting educational material available and collecting patients' opinion about the therapeutic patient educational domains to be covered.

- To plan the European Symposia on RHD to be organized within the 23 rd EHA congress in Stockholm from June 14-17, 2018.

A collaboration among ERN-EuroBloodNet and ePAGs with EHA was established to reinforce the sessions dedicated to patients celebrated within the 23rd EHA congress last June 2018 in Stockholm. This collaboration is result of a request from ePAGs to foster the sessions devoted to patients' advocacy during the opportunity that EHA congress offers as the biggest annual European congress on hematology. The "EHA Capacity Building Meeting" within the 23rd EHA congress took place Thursday, the 14th of June 2018 and was successfully held with a total of 69 attendants.

- To facilitate short stays of health professionals in ERN-EuroBloodNet members with expertise in very concrete diseases and/or procedures to be trained and bring the knowledge from one to another country.

Paroxysmal nocturnal hemoglobinuria (PNH) Aplastic Anemia (AA) were identified identified as area of expertise to be prioritized for the organization of short stays for health professionals for acquisition of expertise given the usual delay in diagnosis due to lack of expertise, which may result fatal for the patient's prognosis. During this period the three highly specialized centers hosting fellows as well as concrete agendas, teachers and focussed topics to be covered by each center has been defined including theory and practice for the promotion of understanding and decision strategy in a field of constant medical progress. The call for participants will be open in the coming period of network implementation.

Specific Objective 4. Provide inter-professional consultation by sharing of expertise and safe exchange of clinical information

- To gather and report to the EC the feedback and impressions from the experience of the first ERN-EuroBloodNet CPMS users during the pilot phase.

ERN-EuroBloodNet participated in the pilot phase of the platform with the introduction of the first real patients. A total of 12 ERN-EuroBloodNet experts participated in the pilot phase with the enrolment of 6 patients. A report including the feedback from the first users was provided to the EC.

- To promote the use of the CPMS among the members of the network

In order to ensure an efficient and effective implementation of the CPMS, ERN-EuroBloodNet has identified as first critical points to a) Have a sufficient number of active users willing to provide advice in the open panels and b) Ensure the most adequate classification of RHD in the “Preferences” area as the key step for users to be selected as panel members based on their expertise.

In line with the strategy, dedicated efforts have been focussed to promote the use of the CPMS among the community, with a result of 55 CPMS experts accounts created and 12 open panels.

On the second point, a new grouping of disease categories for each subnetwork to be included in the “Preferences” section has been proposed to the CPMS Central IT based on an analysis performed by the coordination team with the participation of 6 ERN-EuroBloodNet experts. The exercise gathered concrete needs for each of the category.

Specific Objective 5. Foster European cooperation in highly specialised procedures for diagnosis, innovative treatments and research

- To establish the state of the art of clinical trials at EU level allowing the identification of gaps where action is more needed

A desk research has been conducted on Clinicaltrials.gov for the analysis of the state of the art of clinical trials on rare hereditary anaemias (RHA), with the identification of total of 256 CTs for the 105 disorders. Results have shed light on the disorders that are not covered by any CTs, representing 75% of the RHA.

Those results demonstrate urgent need to improve the access to CTs of patients affected by RHA across EU. ERN-EuroBloodNet has therefore started to conduct academic CTs in very rare diseases in which pharmaceutical companies have not planned CT, ie. Luspatercept and Senicapoc.

- To facilitate European epidemiological surveillance of RHD by promoting the creation of a European registry of patients affected by a RHD

ERN-EuroBloodNet has promoted the participation of expert centres and national registries in RADeep as the initiative endorsed by both ERN-EuroBloodNet and the European Hematology Association (EHA) aiming at promote clinical and basic research at the European level on rare anaemia, while ensuring the application of recommendations released by the EU-RD-platform.

1.7. Description of the activities carried per WP

- Work Package 1

Describe the activities carried out in WP1 during the reporting period giving details of the work carried out by each beneficiary involved. Describe corresponding evaluation activities and results. Describe dissemination activities and their results.

WP1 - COORDINATION AND EVALUATION

ERN-EuroBloodNet coordination is in charge of establishing the management programme for the efficient overall coordination of the network necessary for fulfilling ERN-EuroBloodNet's outcomes and specific objectives. Coordination methodology refers to all aspects concerning the tasks management, quality insurance and assessment of their interactivity, progress and final results. At the beginning of the period, ERN-EuroBloodNet coordination established the Multiannual Work Plan (MWP) in line with the FPA and updated based on the achievements from the previous year – **Milestone 1 Multiannual work plan (MWP) M (Mo 1)**

ERN-EuroBloodet Management and Coordination has been organised according to the following tasks:

Task 1 Organisation of ERN-EuroBloodNet meetings

ERN-EuroBloodNet Coordination team arranged and organised the Board of the Network meeting and Scientific and Strategic Board meetings for this period, organised to create and maintain the co-operation momentum target-driven.

ERN-EuroBloodNet Coordination team ensured official invitation to all involved stakeholders and defined meetings location and agenda. ERN-EuroBloodNet manager was in charge of providing the agenda in advance and distributing main outcomes for approval immediately after the meeting. Certificates of attendance were sent to participants under request.

The Scientific and Strategic Board (SSB) meetings have been held every 6 months, where SSB members presented the results of their tasks and the planned activities for the next months. In total, two SSB meetings and one Board of the Network (BoN) meeting have been held during this period:

- 3rd SSB meeting - Brussels, 5th April 2018 - 25 attendants
- 4th SSB meeting – Brussels, 27th September 2018 – 21 attendants
- 2nd Board of the Network (BoN) meeting – Paris, 8th November 2018 – 73 attendants

The 2nd ERN-EuroBloodNet meeting represented a big step forward in the network implementation, where not only main results and next steps were presented, but also where the active willingness of participation and commitment of our members was consolidated.

An informative bulletin with the ongoing projects and main results from the BoN meeting is available in the ERN Collaborative platform together with ppt presentations.

Milestone 4 Minutes on BoN meeting (Mo 9), Milestone 5 Minutes on 3rd SSB meeting (Mo 1), Milestone 6 Minutes on 4th SSB meeting (Mo 7)

Milestones concerning the production and distribution of outcomes from BoN and SSB meetings were achieved successfully after each meeting.

Task 3 Monitoring exercises

In order to facilitate the control of the risks of schedule and technical aspects the coordination team prepared a ERN-EuroBloodNet calendar in order to determine:

- Work phases and time requirements to develop each task
- TFA and/or specific board involved in the task (SSB, BoN, coordination team…)
- Deliverables
- Milestones
- Indicators

This calendar was presented and discussed with TFAs coordinators through specific TFA teleconferences arranged in order to consolidate the main steps to follow.

In addition, the calendar was presented at each ERN-EuroBloodNet SSB meetings held during the first year in order to show how the progress was ongoing and ensure the time adherence of the tasks.

Moreover participation of each member representatives in the different activities performed in the network has been monitored in order to assess their level of response.

Milestone 2 and 3 Report on monitoring exercises including a specific section for evaluation (Mo 6 and 12)

Participation of members in the different activities organized by the network (eg. Face to face meetings, questionnaires…) has been regularly monitored in order to control both, members and scientific and strategic board members active involvement in ERN activities. (See 1.4. Overview of the evaluation activities and results – Participant or partner feedback).

Task 4 Preparing the annual report for its submission to CHAFEA

The objective of this task was the preparation on due time of the annual final report (M12+2) including the deliverables for the period.

Based on the Grant Agreement for ERN-EuroBloodNet and the guidelines published by the EC, all the templates and supportive documentation for the reporting of the project were elaborated by the ERN-EuroBloodNet coordination team.

The Deliverables were successfully submitted to the European Commission in due time.

The final report has been prepared to be submitted to the European Commission by 13th May 2019.

New Task 5. Sickle Cell Disease (SCD) ERN-EuroBloodNet Patients Network

ERN-EuroBloodNet is establishing a European SCD Patients network that will represent the umbrella of SCD National Patients Organizations in Europe with the objectives of:

1) Give a solid representation to SCD Patients in Europe.

2) Create the premises for the development of a strategic alliance for the collaboration across Europe of the SCD patients.

The European Network of SCD patients' organisations will be authonomous and managed by members and national patients representatives. Each country will have 2 spokesmen in representation of all their national patients' organizations. Among all

spokesmen a representative will be trained to become an ePAG for the ERN EuroBloodNet for SCD.

Next steps include:

- Italian and French national Meetings of SCD patients associations
- Probably first European Meeting the day before or after the BoN, the 14th of November

- Work Package 2

WP2 - DISSEMINATION

During the second year of the network the following activities have been implemented in line with the defined objectives for the period and in agreement with the ERN-EuroBloodNet dissemination plan established in the first year of the network:

Task 1 Update the dynamic Stakeholders Directory (SD) in each Member state and at European and International level

The SD created during the first year of the network through ERN-EuroBloodNet inventory of members and experts has been expanded at ERN-EuroBloodNet website restricted section with special efforts to identify a) health professionals involved in the provision of care within the multidisciplinary teams of Centers of Expertise and b) health professionals experts in the very rare diseases. The experts who have already created their profiles in the restricted section of the website are available at the specific ERN-EuroBloodNet Members section. Also experts can be found through the Disease search tool also implemented this year.

Task 2 – ERN-EuroBloodNet communication material

2.1 Dissemination of first year of implementation results

A pack for dissemination on the ERN-EuroBloodNet 1st year of implementation results was produced at the beginning of this period in order to be shared with all stakeholders. The dissemination pack included:

- 200 ERN-EuroBloodNet pendrives with the Final report, Deliverables and dissemination material generated (leaflet, flyer, poster, official presentation…)
- 200 ERN-EuroBloodNet Lanyards
- 200 ERN-EuroBloodNet Tote bags
- 500 ERN-EuroBloodNet pens
- 250 ERN-EuroBloodNet Notebooks, following the design line of the leaflets and flyers and including in the first pages the main results obtained in the first year of implementation of the network.

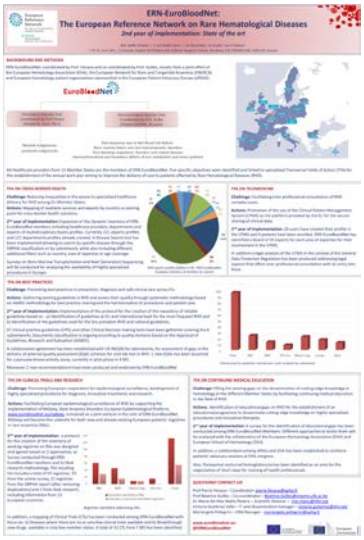
The dissemination pack was distributed among the ERN-EuroBloodNet stakeholders at:

- 23rd Congress of the European Hematology Association (EHA), June 14 - 17, 2018, Stockholm, Sweden
- ERN-EuroBloodNet 2nd Board of the Network meeting, November 8th 2018, Paris, France.

2.2 Update and creation of new ERN-EuroBloodNet dissemination material

ERN-EuroBloodNet leaflet and flyer

ERN-EuroBloodNet leaflet and flyer were produced during the first year of the network offering a professional and attractive look of the network complexity to the different audiences in order to both, contextualize a long term effort that is consolidating an endurable network across Europe, and spread the existence of ERN-EuroBloodNet to the world. ERN-EuroBloodNet hard copies leaflet and a flyer have been successfully disseminated during this period among educational and scientific events. They are also available at ERN-EuroBloodNet website. Update and translation of leaflet and flyer to Dutch, French, Germany, Italian and Spanish are currently under development to maximize the diffusion of the network.



ERN-EuroBloodNet poster

A new DINA0 Poster presenting the governance of the network, subnetworks as well as transversal fields of action (TFA) was produced aiming to present the main concrete areas of active action in the network. The poster was designed to include for each of the TFA a) Challenges encountered, b) Actions so far, and c) 2nd year of implementation results.

Contacts for the coordination team are also provided. EC and CHAFEA logos visibility have also been ensured.

The poster has already been displayed in a number of events and distributed via the ERN Collaborative platform.

ERN-EuroBloodNet ppt

An updated power point presentation on ERN-EuroBloodNet state of the art was presented and shared after the Board of the Network meeting in order to facilitate the dissemination of the network to a wide range of public by summarizing most relevant challenges and achievements.

Different from the general presentation produced during the first year of the network, this power point includes 17 slides focussed on the current active lines of work under the each of the specific TFAs, as well as the main outcomes achieved so far. It has been disseminated by e-mail to all the Board of the Network and has been published in the ERNs Collaborative platform.

Additionally it is important to mention that members are welcomed to contact Coordination team in case specific information or slides on the specific actions are required to be presented in their talks.

ERN-EuroBloodNet Informative Bulletin on Ongoing Projects

During ERN-EuroBloodNet second year of implementation 15 concrete projects have been launched focused on the different Transversal Fields of Action and rare hematological diseases areas where members are already actively involved.

The 2nd ERN-EuroBloodNet Board of the Network (BoN) Meeting was held 8th of November 2018 with more than 70 participants, providing the perfect opportunity to show the audience the most relevant results obtained so far, while providing all the information required on how to become involved in concrete projects of their interest within the areas of Cross border health, Best practices, Continuing medical education, Telemedicine and Clinical trials and research.

In the last months there have been progresses in the different concrete actions while also the 4th Conference on ERNs was held, reaching important transversal issues to all ERNs.

Following the information provided in the 2nd BoN meeting and together with the most important information provided in the 4th Conference on ERNs, an Informative Bulletin on ERN-EuroBloodNet Ongoing Projects for members was produced and sent to the members. Bulletin included the main outcomes from the ERN-EuroBloodNet 2nd BoN Meeting updated with:

- List of Ongoing Projects and Coordinators
- Current State of the art of Ongoing Projects
- Updates from the 4th Conference on ERNs

ERN-EuroBloodNet Newsletter

ERN-EuroBloodNet newsletter has been designed in order to transmit directly to the members the most relevant RHD news while keeping them updated with the main achievements of ERN-EuroBloodNet, maximizing the impact of ERN-EuroBloodNet activities through the stakeholders. The newsletter will be also freely available on the website.

ERN-EuroBloodNet Twitter account

@ERN-EuroBloodNet Twitter account registers 626 Tweets, 467 followers (207 more than last year), and 152 followed. Active interactions are given among the rest of ERNs, EU Health, projects as EJP on RDs, ELIXIR or RD-Connect, patients' associations as EURORDIS or Myeloma Europe, scientific associations as EHA or ESH (European School of Hematology) among many others.

Task 3 - Update and expansion of the ERN-EuroBloodNet website (www.eurobloodnet.eu)

ERN-EuroBloodNet website has become the main tool of dissemination of the network since its release last July 2017, providing the skeleton of the complex structure that ERN-EuroBloodNet represents by endorsing specific dedicated sections to the all the activities and tools developed by the networks while ensuring interoperability with other platforms.

ERN-EuroBloodNet website has been conceived as the on-line platform that provides not only the door of access to ERN-EuroBloodNet dynamic and public inventory of members and experts but also to the main tools developed and implemented during the running time of the network.

In this context, ERN-EuroBloodNet website can be understood as two-side online platform with two main objectives:

- ERN-EuroBloodNet website as the main tool for dissemination of the goals and achievements to boost public awareness of the network.

- ERN-EuroBloodNet website as the infrastructure (web portal and database) for accessing the Inventory of ERN-EuroBloodNet members and experts profiles

New sections and specific target-actions engines have been implemented in this period for the exploitation of the data collected while keeping the website in an evolving environment attending to the network's need.

3.1 New section – Privacy Policy

ERN-EuroBloodNet is committed to protect users' while providing a safe online experience in accordance with the Regulation EU 2016/679 of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation). In this context, ERN-EuroBloodNet Statement of conditions of use and Privacy applying to the website and explaining data collection and usage has been publicly available at the website.

3.2 Updates on the ERN-EuroBloodNet inventory - Profiles applications' forms

Updates on the ERN-EuroBloodNet inventory of experts and members encompasses:

- Revision and update of ORPHA classification for Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis subnetwork
- Improvement in the interface for the selection of diseases included in ORPHA classification
- ERN-EuroBloodNet disease search engine design and implementation
- Update on the public visualization of ERN-EuroBloodNet inventory at the website

Full explanation of the updates are detailed in section "**1.2. Overview of the project results – WP 3-TFA 1 – CROSS BORDER HEALTH**" and in the present section "**1.7. Description of the activities carried per WP WP 3-TFA 1 – CROSS BORDER HEALTH**".

Task 4 – Promotion of the use of the ERN Collaborative Platform

The platform developed by the EC provides huge possibilities for an easy communication and sharing of documents among ERN-EuroBloodNet members. The ERN-EuroBloodNet dedicated section in the ERN Collaborative Platform has been used in order to share with ERN-EuroBloodNet members the following documents:

- Poster and Slides presented during the ERN-EuroBloodNet meeting hold during the European Hematology Association (EHA) Annual Congress took place last 14-17 June 2018 in Stockholm
- ERN-EuroBloodNet 1st annual report, including the Technical report and Deliverables produced during the first year of implementation
- Slides presented during the 2nd Board of the Network meeting hold the 8th November 2018.
- ERN-EuroBloodNet informative Bulletin on ERN-EuroBloodNet Ongoing Projects for members with the state of the art (to date January 2019) of the different actions where members can be actively involved.

A total of 53 ERN-EuroBloodNet users are active in the ECP. 11 new users have created their account in this period.

Task 5 – Relations with third parties

5.1 Promotion of collaboration agreements with third parties

In order to create a real network it is essential to create synergies with other ERNs, projects and initiatives working towards objectives complementary to those of ERN-EuroBloodNet. Links for collaborative agreements have been already established and consolidated during this second year:

a) Transversal activities to all ERNs

European Commission and ERNs Coordinators Group

The ERNs coordinators groups (ERNs CG) is formed by the 24 coordinators of ERNs, and during the second year it works under the coordination of Prof Franz Schaefer (ERKNET).

In order to address the different frames of action, 6 Working Groups (WG) were established, where each ERN could participate, through their coordinators or any of their members, up to 3 WG.

ERN-EuroBloodNet decided to participate in WP on Research with Pierre Fenaux and Uwe Platzbecker as representatives, WP on Cross border health and brexit with Raffaella Colombatti as representative and WP 5 on Knowledge generation with Béatrice Gulbis and Maria del Mar Mañú as representatives. Additionally, in the context of WP 5, a new ERNs task force has been created in order to work on the taxonomy of Clinical Practice Guidelines and other related documents. Scientific director, Maria del Mar Mañú, and TFA on Best practices coordinators, Achille Iolascon and Luca Malcovati, are the representatives for ERN-EuroBloodNet.

ERN-EuroBloodNet has been present in all the ERNs CGs meetings organized by the EC aiming to update coordinators in the main issues concerning the operational management of the networks. ERN CGs meetings organized in this period have been the following:

1. 4th meeting of the ERNs CG, 5th March 2018 in Brussels - Attended by ERN Co-coordinator, Béatrice Gulbis, and ERN Scientific Director, Maria del Mar Mañú.

2. 5th meeting of the ERNs CG, 25th June 2018, Brussels - Attended by ERN manager, Mariangela Pellegrini.

3. 6th meeting of the ERNs CG, 20th November 2018, Brussels – Attended by ERN Co-Coordinator, Béatrice Gulbis, and ERN Scientific Director, Maria del Mar Mañú.

Moreover, ERN-EuroBloodNet team was also present at the 4th Conference on ERNs that took place 21-22 November 2018 in Brussels, where ERN coordinator, Pierre Fenaux, presented during the Plenary session: Round table IV."ERNs' Main challenges for the future", the main challenges to be faced by ERNs in the experience of the network.

ERN-EuroBloodNet was represented during the 4th ERNs Conferences by:

- Pierre Fenaux: ERN-EuroBloodNet Coordinator and Oncological hub coordinator
- Béatrice Gulbis: ERN-EuroBloodNet Co-coordinator and Non-Oncological hub coordinator
- María del Mar Mañú Pereira: ERN-EuroBloodNet Scientific Director
- Victoria Gutiérrez Valle: ERN-EuroBloodNet IT and dissemination manager
- Mariangela Pellegrini: ERN-EuroBloodNet Manager
- Fahed Ahssini: ERN-EuroBloodNet Operational Helpdesk

- Patricia Aguilar-Martinez: Transversal Field of Action on Continuing medical education coordinator for the non oncological diseases
- Sebastian Wittnebel: Representative of the Transversal Field of Action on Continuing medical education coordinator for the oncological diseases
- Antonio Piga: Transversal Field of Action on Clinical Trials and Research coordinator for the non-oncological diseases
- Amanda Bok: ePAG for Haemophilia, Rare bleeding-coagulation disorders and related diseases subnetwork coordinator, and Transversal Field of Action on Best Practices coordinator
- Pierre Aumont: ePAG for Chronic Lymphocytic and Waldenström disease, and Leukemia and Lymphoid malignancies subnetwork coordinator

A piece of news on the Conferences is available at:

1. Summary report and Video recording of the 4th Conference on European Reference Networks available!

Cross-ERN Task Force meeting on eHistopathology

EpiCare and ERKNet joined forces to tackle this challenge by creating a cross-ERN Task force on the topic. ERN-EuroBloodNet representatives actively participating in the task force are: Alessandra Renieri (IT), Monika Prochorec-Sobieszek (PL) and Kikkeri Naresh (UK).

European Commission – Joint Research Center (JRC)

Since ERDRI providing the first tools to promote the harmonization and interoperability among registries, the following workshop has been organized during this period:

1. EU Rare Diseases (RD) Platform: Second training workshop on the European RD Registry Infrastructure (ERDRI) tools. 8-9 March 2018, Milan - Attended by ERN IT and dissemination manager, Victoria Gutierrez.

European Joint Programme (EJP) on Rare Diseases

ERN-EuroBloodNet has established official collaborations to participate in four of its pillars by ERN-EuroBloodNet representatives: Achille Iolascon, Marina Kleanthous, Patricia Aguilar Martinez and Paola Bianchi.

The first 1st joint call for EJP rare diseases (JTC 2019) on the specific topic "Research projects to accelerate diagnosis and/or explore disease progression and mechanisms of rare diseases" was opened in December 2018. The proposal "Innovative Diagnostic Evaluation of rare Anaemias (IDEA)" was submitted including several ERN-EuroBloodNet members under its consortium on the 15th February 2019.

b) Rare Hematological Diseases

ORPHANET

ERN-EuroBloodNet has established a collaboration for the implementation of ORPHA classification for RHD at the back office of ERN-EuroBloodNet website prior revision of the classifications by subnetworks coordinators. Collaboration will be strengthen with the aim of contributing to the improvement of the Orphanet nomenclature.

European Hematology Association (EHA)

The EHA represents one of the core pieces for the creation of ERN-EuroBloodNet and is fully devoted to contribute in the activities undertaken by the network related to the Continuing Medical Education.

European School of Hematology (ESH)

ESH is fully devoted to contribute in the activites undertaken by the network related to the Continuing medical education.

European Joint Action on Rare Cancers (JARC)

JARC has established collaborations with the three ERNs covering rare cancers in order to joint efforts towards operational solutions and professional guidance in the areas of quality of care, epidemiology, research and innovation, education and state of the art definition on prevention, diagnosis and treatment of rare cancers.

The collaboration of JARC and ERNs, linking information to JARC website and the leaflet produced are available in the following piece of news:

1. Joint Action on Rare Cancers (JARC) and ERNs

In addition , a face to face meeting with JARC, PaedCan, EuroBloodNet and EURACAN was held the 8th February 2019 in order to discuss on common approaches on Guidelines, research and CPMS actions for rare cancers. Pierre Fenaux and Mariangella Pellegrini attended the meeting. Prof. Fenaux had the opportunity to present ERN-EuroBloodNet and potential areas of involvement with JARC.

c) Patients

EURORDIS

ERN-EuroBloodNet has strengthen its relationships with patient associations through a close collaboration of EURORDIS ePAGs. In addition, the generation of contents for social networks consolidates and creates new contacts with patients through these organizations.

ERN-EuroBloodNet has also collaborated in the dissemination of the activities organized by for the Annual Rare Diseases Day. The dissemination has been mainly done through ERN-EuroBloodNet website and twitter by posting news and contributing to the Rare Disease Day movement.

1. Rare Disease Day 2019 "Bridging health and social care": Get involved!
2. EURORDIS Black Pearl Awards 2019

ERN-EuroBloodNet has been also present at the biennial European Conference on Rare Diseases and Orphan Products organized by EURORDIS on 10-12 May 2018, Vienna. Mariangela Pellegrini, ERN-EuroBloodNet manager, participated at the ECRD with a presentation focused on Crossborder health titled "ERN-EuroBloodNet's overview for reaching an equal access to care for rare haematological diseases patients across European Union' Members States". A piece of news was also published when the special supplement was released on the Orphanet Journal of Rare Diseases including all the abstracts presented on the congress:

1. The special supplement on the 9th European Conference on Rare Diseases & Orphan Products (ECRD)

Patient's Associations

The cooperation with these entities includes listing a growing number of Associations in the ERN-EuroBloodNet website patient's advocacy section. In addition, further initiatives where ERN-EuroBloodNet ePAGs representatives have collaborated are:

#ProtectERNs initiative

ERN-EuroBloodNet has also participated in the campaign #ProtectERNs to highlight the importance of UK's involvement after Brexit. In this context, Maria Piggin, ERN-EuroBloodNet ePAGs for the Paroxysmal nocturnal hemoglobinuria (PNH) and Chair of PNH Support, and Sophie Wintrich, ERN-EuroBloodNet ePAGs for Myelodysplastic syndromes (MDS) and CEO of MDS UK, both based in London, participated in a blog

written for the Protect ERNs website with four examples of ways that rare disease communities in the UK stand to lose if the UK is prevented from continuing to collaborate in ERNs.

1. #ProtectERNs - The impact of Brexit from the Patients affected by Rare Hematological perspective

ePAGs Joint leaflet for patients affected by Rare Cancers

ePAGs representatives for the ERNs covering rare cancers (EURACAN, EuroBloodNet, PaedCan and GENTURIS) have joined efforts under the umbrella of EURORDIS and JARC to produce a leaflet for patients explaining the ERNs and how they will help patients, ePAGs advocacy groups and explaining the main coverage of each of the 4 ERNs.

5.2 Attendance to European Rare diseases meetings and workshops

ERN-EuroBloodNet members are devoted to spread the messages and services of the network in every forum that might be relevant to strengthen the network. Meetings on RHDs are frequent around Europe and the ERN-EuroBloodNet members work to have a presence in the most relevant ones. Most relevant events with an active participation of ERN-EuroBloodNet have been during this period:

- European Hematology Association (EHA) congress, June 14 - 17, 2018, Stockholm
  - Presentation of the network at the ePAGs Capacity Building Program by Coordinator, Pierre Fenaux.
  - Presentation of the network at the Red blood cell and iron EHA working group, by Scientific Director, Maria del Mar Mañú
  - Dedicated booth for ERN-EuroBloodNet dissemination, Victoria Gutierrez and Mariangella Pellegrini
- Conference of clinical research network on Sickle Cell Disease, 4th of October 2018, Paris "Sickle Cell Disease, from a Belgian registry to an European" by ERN-EuroBloodNet co-coordinator Béatrice Gulbis, and member representative Alina Ferster.
- European Alliance for Personalised Medicine Congress, 26-27th November 2018, Milan. "ERN-EuroBloodNet: A slidehow on implemented activities for reaching an equal access to highly specialized care across European Member States for Rare Hematological Diseases" by Mariangela Pellegrini
- II Italian Meeting on HCP participating in ERN-EuroBloodNet, 30th January 2019, Rome. The whole network was presented in different lectures by the following members:
  - Raffaella Colombatti - TFA Cross border health actions on non oncological hub
  - Antonio Risitano - Preceptorships on PNH and AA
  - Paola Bianchi and Raffaella Colombatti – ERN-EuroBloodNet inventory of members
  - Domenica Cappellini and Paola Bianchi – RADeep state of the art
  - Luca Malcovati and Achille Iolascon – Actions on Guidelines
  - Matteo della Porta and Antonio Piga- Actions on Clinical trials and research
- Local annual meeting on haemoglobinopathies, 2nd February 2019, Cyprus. "EuroBloodNet activities" by ERN-EuroBloodNet member representative Marina Kleanthous
- European Society for Blood and Marrow Transplantation Board Meeting, Severe Aplastic Anemia Working Party EBMT, 11th February 2019, Frankfurt "Preceptorships on PNH and AA" by ERN-EuroBloodNet member representative Régis Peffault de la Tour

Task 6 - Visibility of ERN-EuroBloodNet and European Commission

6.1. Dissemination of ERN-EuroBloodNet health services among health primary care physicians by conferences

ERN-EuroBloodNet members participate in events oriented to share knowledge and explain the aims and services provided to primary care physicians. Those experts are the first line of interaction with patients, and giving them the right information is essential to offer the right answer to each patient.

6.2. Dissemination of Rare Hematological Diseases by scientific symposiums, workshops…

ERN-EuroBloodNet members are often invited to offer a talk in scientific meetings of different kinds. Every opportunity to present ERN-EuroBloodNet to an audience is important to make the network stronger.

6.3. Recognition ERN-EuroBloodNet and EC logo in each dissemination activity.

Each and every action undergone by ERN-EuroBloodNet is acknowledged with the ERN-EuroBloodNet official logo and the corresponding EC recognition. The role of the EC is crucial to the existence of the network and it is mandatory to all partners to put it forward in any action undergone by ERN-EuroBloodNet. The EC-cofunding logo has been included in: ERN-EuroBloodNet website and dissemination material.

- Work Package 3

WP 3 – TFA 1 – CROSS BORDER HEALTH

ERN-EuroBloodNet Specific Objective 1 linked to TFA1: Improve equal access to highly specialised healthcare delivery for RHD across Europe.

Task 1.1 Mapping of services (clinical and diagnosis) available in Europe for best clinical care

1.1.1 Updates on the ERN-EuroBloodNet inventory of experts and members

ORPHA classification for RHD: Revision and update for Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis subnetwork

The ORPHA classification for the diseases encompassed in the Hemochromatosis (HH) and other rare genetic disorders of iron metabolism and heme synthesis subnetwork has been reviewed for the inclusion of porphyrias (defects of heme synthesis) and ferritinopathies (they are in the differential diagnosis of hypoferritinemias).

At this stage, discussions are still ongoing in order to create a consensus among experts. Once the final consensous is achieved, feedback will be provided to ORPHA. In the meantime, the second version of the ORPHA classification for the subnetwork has been provided to the Website developers and is currently being programmed for its availability in the ERN-EuroBloodNet website inventory.

Improvement in the interface for the selection of diseases included in ORPHA classification

A new interface for the selection of the diseases of expertise through the ORPHA classification has been designed in order to expand the possibility of selecting diseases through all the levels of the classification without the current limitation to the fourth level of ORPHA classification. In addition, the new interface offers a more

attractive visibility of the diseases selected facilitating the readability and selection by the experts.

The new interface will be available in the Department profiles for the selection of diseases covered by the department, and Experts' profiles for the selection of the diseases of expertise.

ERN-EuroBloodNet disease search engine

A Disease Search tool was designed to exploit the data gathered through the inventory of ERN-EuroBloodNet members and experts. The engine was envisaged to search for experts based on the information gathered through their individual Experts' profiles. The following searching parameters were defined for the engine implementation:

Search experts by:

- Specific diseases: Through an engine for searching in the whole ORPHA classification implemented at the back office of the website and inventory.
- Subnetwork: To create a more general query focused on the diseases covered by a subnetwork.

Additional filters based on the Experts' profiles fields:

- Patients age coverage: Pediatrics, adults, ageing.
- Area of expertise: Prevention and genetic counseling , diagnostics, treatment and care
- Country: To be selected from the list

Public visualization of ERN-EuroBloodNet inventory at the website – Update

According to the new updates implemented in the ERN-EuroBloodNet inventory, the Members section accessible at the top bar of the ERN-EuroBloodNet website has integrated a submenu including "Member and representatives", "List of experts" and "Search experts".

1.1.2 State of the art of Bone marrow transplantation and Next generation sequencing for non-oncological rare haematological diseases

In agreement with the priorities identified in the RHD field for the establishment of cross-border agreements, two online surveys were identified to be conducted among ERN-EuroBloodNet members with focus on HSP key for the diagnosis or treatment of many non-oncological RHD and presenting high inequalities for its access among MS: Bone marrow transplant (BMT) and Next generation sequencing (NGS) for non-oncological disorders.

Survey on Bone marrow transplantation for non-oncological RHDs

Survey included four main sections:

a) Responder data: name, surname, mail, institution, role, area of expertise

b) BMT need: To assess diseases for which the respondent consider the BMT for the correct management of the patients

c) BMT availability: To analyze for which non-malignant RHDs and patients' age the respondent's center offers the BMT. If BMT is not offered, reason is also requested for their assessment.

d) State of the art of BMT cross-border: To assess if referrals to other centers are ever considered when necessary and if a standardized procedure is in place in such

cases. Problems experienced in the referral of patients are also requested for their analysis.

Survey on Next Generation Sequencing and other Advanced technologies for non-oncological RHDs

Survey included four main sections:

a) Responder data: name, surname, mail, institution, role, area of expertise

b) NGS/Advanced technologies need: To assess which advanced technologies and for which disorders the respondent consider necessary for the correct management of patients.

c) NGS/Advanced technologies availability: To analyze if responder's center performs NGS/Advanced technologies and for which non-malignant disorders. If these technologies are not offered, reason is also requested for their assessment.

d) State of the art of NGS/Advanced technologies cross-border: To assess if

- Referrals of samples to other centers are considered when necessary, with what objective and the procedure in place in such cases.

- Samples are received from other centers, with what objective and the procedure in place in such cases.

Task 1.2. Establishment of a model for cross border referral system - Directive 2011/24/EU

ERN-EuroBloodNet legal analysis aims at perform a practical exercise analyzing the implementation of the directive and the possibilities for bilateral agreements in at least 6 MS expected to require them based on previous identified GAPs in the delivery of care for RHD (Task 1.1). This practical exercise could be understood as a pilot that may further contribute to remove barriers hampering cross-border care initiatives.

In this context, a task force has been created and an action plan defined including the analysis of the Collaboration agreement for BMT on SCD among Italy and Ireland for the identification of the critical and most conflictive issues for its establishment and its translation into a practical tool.

- Work Package 4

WP 4 – TFA 2 – BEST PRACTICES

ERN-EuroBloodNet Specific Objective 2 linked to TFA2: Promote best practice in prevention, diagnosis and clinical care across EU

Task 2.1. Create a comprehensive public database of reliable guidelines

2.1.1 Expansion of the List of international guidelines and recommendations

The first list of international guidelines and recommendations was analyzed in terms of coverage of the different diseases encompassed by the network. Given the expertise of the subnetworks coordinators, the scope of the list was well balanced through the different RHDs, nevertheless, it was agreed to conduct a revision by additional experts identified in the field in order to produce a second version as extensive and comprehensive as possible. Special efforts were focused on the gathering of more CPGs for the oncological disorders given the relatively low number compiled in the first exercise.

2.1.2 Classification of guidelines and recommendations based on Quality domains

The domains on which guidelines and recommendations compiled were classified were defined as follows:

Domain 1: Scope and purpose

Each document shall be classified based on the objectives and clinical questions, adopting the following items:

1. Prevention
2. Diagnosis
3. Treatment
4. Prevention and diagnosis
5. Diagnosis and treatment
6. Prevention, diagnosis, treatment

Domain 2: Patients' involvement

The composition of the guideline / recommendation development group shall be evaluated with reference to the involvement of patient advocacy organizations patients.

Domain 3: Rigour of development.

The methodology adopted to develop the guideline / recommendation shall be assessed according to the following scale.

Level A: Evidence- and consensus-based guidelines / recommendations

The guidelines / recommendations were developed adopting a grading system for strength of recommendation involving assessment of the quality of scientific evidence. The most commonly adopted systems include GRADE (Grades of Recommendation Assessment, Development and Evaluation) (http://www.gradeworkinggroup.org/) or SIGN (Scottish Intercollegiate Guidelines Network) (https://www.sign.ac.uk). Briefly, these systems involve a systematic review of the literature and synthesis of evidence with assessment of the quality of scientific evidence based on study design (i.e. randomized clinical trials, case-control or cohort studies, non-analytic studies, e.g. case reports, case series), study quality and consistency across study. Recommendations were ranked based on the strength of supporting evidence. These approaches may or may not be explicitly coupled with formal consensus development techniques (e.g. Delphi method, nominal group technique).

Level B: Consensus-based guidelines / recommendations

The guidelines / recommendations were developed based on consensus among experts adopting formal consensus development techniques without including a systematic review of the literature and synthesis of evidence and a grading for strength of recommendation. Formal consensus development techniques include the Delphi method or nominal group technique. Briefly, these communication techniques are aimed at providing an unbiased and independent process of consensus within a panel of experts through the use of questionnaires and structured face-to-face meetings addressing key clinical questions relevant to the guideline / recommendation purpose.

Level C: Expert opinion

The guidelines / recommendations were entirely based on opinion by a variable number of experts without systematic review of the literature and formal consensus development techniques.

Subnetworks coordinators were requested to coordinate the action on their area of expertise. For this task, TFA on best practices coordinators and Coordination team circulated subnetworks-specific Assessment templates, including:

- Objective and Instructions: with the definition of the levels for each of the three domains
- Assessment template: list of guidelines and recommendations including disease coverage and template for completing the three domains
- Subnetwork task force: list of experts per disease identified as potential contributors for the task

Task 2.2. Assessment of the level of awareness and implementation of existing guidelines

2.2.1 Diseases and indicators identified for assessment of the holistic clinical management of RHD conditions including prevention, diagnostic tests, treatment and follow up.

In order to gather the first indicators for the assessment process, TFA on best practices coordinators and Coordination team circulated to the subentworks coordinators Assessment templates subnetworks-specific, including:

- Objective: To assess at the level of implementation by Member State guidelines/recommendations for a selected disease/condition which due to several reasons (prevalence, cost..) is expected to be poor or not completed implemented.
- Section to indicate Disease/condition selected
- Section to explain why this disease/guideline have been selected for assessment of implementation? (Please, identify the items expected not to be full implemented at the EU-MS level)
- Section to list 5 Clinical outcome indicators

2.2.2 Assessment of the implementation of the Consensus recommendations on the diagnosis of pyruvate kinase deficiency

The methodological approach for the assessment has been defined based on the identification of centers performing PK diagnosis and their facilities, and a parallel action to establish the External Quality Assessment on PK diagnosis.

a) Mapping of centers performing PKD diagnosis and facilities for accurate diagnosis and genetic characterization

In order to map European centers performing PKD diagnosis and their facilities a first survey was produced with the objectives to:

- Identify the European medical centres concentrating PKD patients and estimate the number of active PKD patients and with genetic diagnosis
- Identify the European medical centres offering diagnosis facilities for accurate PKD diagnosis and genetic characterization
- Create an up-to-date inventory of medical centres and services available for PKD

The survey included 4 main sections:

a) Organization data

b) Patients' data: Number of PKD patients currently in follow-up, % genotyped, new number of patients per year, participation to any type of patients' registry

c) PKD diagnosis – Part A PK enzyme activity: number of diagnosis tests, method, availability within the medical centre or externalized.

d) PKD diagnosis – Part B *PKLR* genetic analysis: implementation of *PKLR* genetic analysis, availability within the medical centre or externalized.

The complete survey is available at the ERN-EuroBloodNet website

The survey was implemented through an on-line application within the dedicated section of ERN-EuroBloodNet website, allowing the creation of the up-to-date inventory on medical centres and diagnosis facilities and the permanent access to the survey in order to update information from already listed centres or add new centres.

b) Establishment of the External Quality Assessment on PK diagnosis in collaboration with UKNEQAS

During the 1st year of ERN-EuroBloodNet implementation, a collaboration was established with UKNEQAS for a) the analysis of the state of the art of External Quality Assessment for the RHDs diagnosis and b) promote the establishment of schemes for RHD where gaps are identified.

One of the outcomes from the previous period of implementation was the identification of PK assay as high priority for EQA development given the huge inequalities on its performance across MS.

- Work Package 5

WP 5 – TFA 3 – CONTINUING MEDICAL EDUCATION

ERN-EuroBloodNet Specific Objective 3 linked to TFA3: Disseminate cutting-edge knowledge and facilitate continuing medical education in the field of RHDs

Task 3.1. Identification of educational GAPs survey in collaboration with EHA

3.1.1 ERN-EuroBloodNet questionnaire on Continuing Medical Education

For the conduction of the questionnaire, TFA on CME coordinators and ERN-EuroBloodNet coordination team prepared an Excel including two tasks:

Task 1: List of educational materials available by disease group
An excel sheet was created for each subnetwork for the collection of educational material, including sections to:

- Give the title of the educational material
- Indicate if A- Teaching material or B- Patient Education
- Indicate if A- Available in your centre or B - External material
- Language/s of the material available
- Link or indicate annex (PDF, PPT)
- Select group of diseases covered by the material among the disease-categories defined for each subnetwork

Task 2: Assessment of the educational needs

Four questions were defined to assess educational needs by providing the possibility to express two single binary answers. First concerns the affirmation or denial of a need (yes/no). Second underlines if the need is correlated to CME or therapeutic patient education (patient specific/health professional specific). Three free-text boxes were provided to specify the disease/ the group of diseases, to describe the educational need and why it is required.

The four questions that compile the task 2 are:

- Q1. Do you have specific educational needs in your field of expertise?
- Q2. Do you have specific educational needs out of your field of expertise?
- Q3. What would be – according to your opinion - the unmet educational needs that should be filled by the ERN, in order of priority? (e.g. Teaching material, guidelines, patients' education… Please list a maximum of 5.)
- Q4. Additional comments

Survey was successfully conducted from July to September 2018.

3.1.2 Repository of Sickle Cell Disease Therapeutic Patient Educational material

The survey was designed by ERN-EuroBloodNet coordination team and Angelo Loris Brunetta (ePAG RBC subnetwork coordinator), and prepared in an excel including two tasks:

Task 1: To gather the educational material used/known for SCD.

It gives the possibility of a free-text answer for each Excel box:

- Title of the educational material
- Indicate if A- Available in your patient organization or B - External material
- Indicate if cover: Adult/Pediatric/Transition
- Format (training course, e-learning plateforme, book, article, video, mobile application, interactive game, etc)
- Language/s of the material available
- Link or indicate annex (PDF, PPT)

Task 2: To gather educational needs from the patients' perspective.

1. First free-box question: which is your country of residence?
2. Second question: do you have any specific educational needs?
3. Third question: what would be – according to your opinion - the unmet educational needs that should be filled by the ERN, in order of priority? Please list a maximum of 5.

Survey will be conducted next period of network implementation.

New Task 3.2 Webinars program for health professionals

Webinars and presentations with audio for health professionals have been included in the multi annual-educational programme promoted by ERN EuroBloodNet.

In order to list potential target topics to be covered by the webinars, ERN-EuroBloodNet, within the TFA CME task force has analysed the results from the survey "ERN-EuroBloodNet questionnaire on CME" and the List of international

guidelines and recommendations – "Deliverable 4.1 Report on the comprehensive public database of reliable guidelines".

Task 3.3. Co-organization with the ePAGs of European symposia with interactive patient participation

ERN-EuroBloodnet , ePAGs and the Hematology ePAG Project Management Office has been working very closely with the EHA congress office in the organization of the "EHA Capacity Building Meeting" within the 23rd EHA congress. The Capacity Building meeting was held on Thursday, the 14th of June 2018 and was mandatory for all patient advocates who received the EHA Fellowship. The plenary session agenda was:

- EuroBloodNet and the ePAG (Ananda Plate, ePAG representative)
- Getting the most out of EHA as a patient advocate (Jan Geissler, CML Advocates Network, ePAG representative)
- Introduction to PRO-Tools and QoL-instruments (Fabio Efficace, GIMEMA)
- Reading a scientific poster (Tamas Bereczky, EUPATI)
- Patient engagement in scientific publications (Dawn Lobban, Envision)

Task 3.4. Identification of areas including highly specialized procedures requiring short stays for the acquisition of expertise

Perceptorships aim to discuss AA, PNH, and other related bone marrow failure syndromes and to provide applicants with the fundamental tools for a correct diagnostic and treatment approach to marrow failures, including AA and PNH in children, adolescents and adult patients.

3 or 4 days program will be held in 3 highly specialized centers of the ERN EuroBloodNet. Each preceptorship will be attended by 4 participants.

Highly specialized centers that will host the preceptorships are:

1) AP-HP Hôpital Saint-Louis, Paris, France. Coordinator: prof. Régis Peffault de Latour.
2) University of Naples Federico II, Naples, Italy. Coordinator : prof. Antonio Risitano.
3) Pediatric Hospital - IRCCS Institute Giannina Gaslini, Genoa, Italy. Coordinator: prof. Carlo Dufour.

Teachers, agendas and topics for each short stay have already been defined.

- Work Package 6

WP 6 – TFA 4 – Telemedicine

ERN-EuroBloodNet Specific Objective 4 linked to TFA4: Provide inter-professional consultation by sharing of expertise and safe exchange of clinical information

Task 4.1. Pilot testing of the CPMS

For the participation in the CPMS pilot phase ERN-EuroBloodNet IT and dissemination manager contacted by email ERN-EuroBloodNet members representatives and substitutes providing information on the new release of the platform, its objectives and first steps for its practical use.

Interested members who wanted to participate in the pilot phase received further details on the steps to follow either to enrol a patient, or participate in an open panel.

Once the pilot phase was closed, a questionnaire was produced by the EC in order to be circulated among the pilot users. In order to identify the main areas of improvement and first impressions on the real use of the platform, the questionnaire included the following items:

1) Do you consider that you were sufficiently well prepared in your ERN or HCP to start working with the CPMS? If not, can you please explain why?
2) Do you agree that local administration rights should be attributed to the ERN Coordinator or even on HCP level in order to streamline the access process? If not, can you please explain why?
3) Currently we grant access to CPMS for health professionals in the first place. Do you think that non-health professionals should have access to CPMS under certain conditions? Can you give examples of such non-health professionals? If so, can you briefly describe the tasks and permissions that should be attributed to them?
4) When looking for a patient, were there specific selection criteria that you applied? Can you explain why the specific patient was selected: case, urgency, complexity, other reason? If it weren't to be the pilot phase, would you still have selected the same patient?
5) Did you easily manage to put together a panel of experts to assess your patient file? If not, can you please explain what the difficulty was?
6) How many members were involved in the panel? How many HCPs and how many Member States were represented?
7) Can you inform if the outcome has been prepared and signed-off? If not, why is the assessment still on-going?
8) In case the outcome was signed-off, has the panel been closed? If not, can you please explain why?
9) Can you provide an indication on the duration of the whole process? Would you consider this being a realistic timing?
10) While a number of comments have already been received, do you think that the provided Standardised Consent Form can easily be used for the purpose of ERN patient consultations in your hospital? If not, can you please explain why?
11) If changes needed to be done, do they apply to the layout of the form or rather to the content?
12) Please provide any other comments you may have or suggestions that can help us for further improvement of the CPMS.

The questionnaire was circulated among the ERN-EuroBloodNet participants in the pilot phase. Answers were compiled by the IT dissemination manager and reported to the EC by 15 March 2018.

New Task 4.2 ERN-EuroBloodNet strategy for promoting the wide implementation of the CPMS

In order to ensure an efficient and effective implementation of the CPMS, ERN-EuroBloodNet has identified as first critical points to

1. Have a sufficient number of active users willing to provide advice in the open panels
2. Ensure the most adequate classification of RHD in the “Preferences” area as the

key step for users to be selected as panel members based on their expertise

An ERN-EuroBloodNet strategy for the promotion of the use of CPMS was defined accordingly including:

4.2.1 CPMS promotion and awareness among members

Broader dissemination among ERN-EuroBloodNet members have been performed through:

- Informative bulletins via email, ie. presentation of the CPMS, procedure to get an access account…
- Dedicated sessions at ERN-EuroBloodNet face to face meetings: the Scientific and Strategic Board meetings and Board of the Network meetings.
- Dedicated slides at ERN-EuroBloodNet general presentations at European/National Congresses.

4.2.2 Upgrade of RHD categories in the "Preferences" section

Disease Categories

ERN-EuroBloodNet CPMS helpdesk and coordination team prepared a template including a new proposal of disease categories for each subnetwork based on ORPHA classification. A template was circulated among the Subnetworks coordinators to provide their feedback including:

- The new proposal of the Categories for each subnetwork based on ORPHA classification
- A section to score each of the Categories from 0-5 to rank the need of the CPMS for each category (0- CPMS not needed, 5- CPMS highly needed).
- A section to indicate the type of advice more required for each of the Category: clinical care/diagnosis/both
- A section to indicate if advice more required for pediatrics/adults/both for each category
- A section for the identification of one or two reference persons for each category

New category for highly specialized procedure - Bone Marrow Transplantation for oncological and non ongological disorders

The expertise required for the performance of Bone Marrow Transplantation (BMT) is highly disease-specific dependent in the RHD area. Thus, for instance, Expertise for Sickle cell disorder BMT transplantation is very different from the expertise required for Myeloid malignancies.

Accordingly, a new category will be proposed to be included in the CPMS preferences for non oncological and oncological disorders. This new proposal was included as well in the template to gather the point of view from the different experts.

- Work Package 7

WP 7 – TFA 5 – Clinical Trials and Research

ERN-EuroBloodNet Specific Objective 5 linked to TFA5: Foster European cooperation in highly specialised procedures for diagnosis, innovative treatments and research

Task 5.1. To facilitate European epidemiological surveillance of RHD by promoting the creation of a European registry of patients affected by a RHD

IN line with the EU-RD-Platform, a first analysis of the different strategies to be implemented for the establishment of a central European registry covering all RHD has been undertaken based on the different prevalence of the diseases tackled by the network.

ERN-EuroBloodNet has promoted the participation of expert centres and national registries in RADeep as the initiative endorsed by both ERN-EuroBloodNet and the European Hematology Association (EHA) aiming at promote clinical and basic research at the European level on rare anaemia, while ensuring the application of recommendations released by the EU-RD-platform.

Task 5.2. To promote the participation in clinical trials

5.2.1 Analysis of the state of the art of on-going CTs for rare hereditary anaemias

In order to establish the state of the art of on-going clinical trials for rare hereditary anaemias (RHAs) a desk research was conducted on ClinicalTrials.gov website.

122 “Search terms” covering 105 disorders classified as rare hereditary anemias were established based on ORPHA classification. For each one, the following parameters were included in the search:

a) Study type: Describes the nature of a clinical study. Study types include:

- Interventional studies (also called clinical trials)
- Observational studies (including patient registries)
- Expanded access.

b) Status regarding recruitment:

- Not yet recruiting: The study has not started recruiting participants.
- Recruiting: The study is currently recruiting participants.
- Enrolling by invitation: The study is selecting its participants from a population, or group of people, decided on by the researchers in advance. These studies are not open to everyone who meets the eligibility criteria but only to people in that particular population, who are specifically invited to participate.
- Active, not recruiting: The study is ongoing, and participants are receiving an intervention or being examined, but potential participants are not currently being recruited or enrolled.

For the avoidance of doubt, the following status regarding recruitment were not included:

- Suspended: The study has stopped early but may start again.
- Terminated: The study has stopped early and will not start again. Participants are no longer being examined or treated.
- Completed: The study has ended normally, and participants are no longer being examined or treated (that is, the last participant's last visit has occurred).
- Withdrawn: The study stopped early, before enrolling its first participant.
- Unknown: A study on ClinicalTrials.gov whose last known status was recruiting; not yet recruiting; or active, not recruiting but that has passed its completion date, and the status has not been last verified within the past 2 years.

c) Status regarding expanded access:

- Available: Expanded access is currently available for this investigational treatment, and patients who are not participants in the clinical study may be able to gain access to the drug, biologic, or medical device being studied.

- Temporarily not available: Expanded access is not currently available for this intervention but is expected to be available in the future.

- Approved for marketing: The intervention has been approved by the U.S. Food and Drug Administration for use by the public.

For the avoidance of doubt, the following status regarding recruitment was not included:

- No longer available: Expanded access was available for this intervention previously but is not currently available and will not be available in the future.

d) Age group: A type of eligibility criteria that indicates the age a person must be to participate in a clinical study. This may be indicated by a specific age or the following age groups:

- Child (birth-17)

- Adult (18-64)

- Older Adult (65+)

e) Phase: The stage of a clinical trial studying a drug or biological product, based on definitions developed by the U.S. Food and Drug Administration (FDA). The phase is based on the study's objective, the number of participants, and other characteristics. There are five phases:

- Early Phase 1 (formerly listed as Phase 0)

- Phase 1

- Phase 2

- Phase 3

- Phase 4

- Not Applicable is used to describe trials without FDA-defined phases, including trials of devices or behavioral interventions.

Results for each search term were download in comma-separated values including All Available Columns. This includes over 20 columns such as Status, Conditions, Interventions, Study Type, Phase, and Sponsor/Collaborators. Comma-separated values format save each study as a separate line in the file, with commas as delimiters, or spacers, between each field. This format is useful for importing study information into spreadsheets and databases.

Information obtained was analyzed to establish the number of on-going clinical trials focused on each condition, type of interventions, geographical coverage and ERN-EuroBloodNet members involvement. Duplications were removed and disease focus was checked for consistency.

5.2.2 ERN-EuroBloodNet sponsoring CTs

EuroBloodNet will carry out trial promotion and data monitoring. The main sponsor for each trial will be the university hospital of the principal investigator. Participation of other EU countries will be possible by defining delegate sponsors in those countries (generally university hospitals), according to the EU directive on clinical trials. We will also cooperate closely with companies for drug storing and shipping, and for pharmacovigilance.

1.8. Follow-up of recommendations and comments from previous review(s)

The follow up of the recommendations pointed out last year are the following:

“We would plan better the timing for developing the protocols, contents, architecture of the platforms. Face to face meetings are very valuable and necessary but more frequent follow-up of activities is needed by coordination through phone and video conferences with involved members in order to ensure that activities are develop as planned.”

In general terms we have improved the timing for the implementation of the milestones and activities to be carried out during this period. Coordination team has focussed efforts in better planning both face to face and online meetings, while keeping track of the calendar prepared for the monitoring of all the SGA actions, ensuring the lowest delay as possible in the deployment of the protocols, contents and architecture of the platforms.

1.9. Deviations from Annex 1

Explain the reasons for deviations from Annex 1, the consequences and the proposed corrective actions

In general terms we can say that we have followed the working plan and fulfilled most of the tasks and activities defined for this period.

As already pointed in the section “1.3 Project results and visibility – Major problems and lessons learned” one of the issues faced during the second year of the network was to overcome the problems faced with the website developers for the upgrade of the ERN-EuroBloodNet members profiles.

The impact was minimized as much as possible by the coordination team, who a) contacted a new company for the taking over of the website and inventory of members and b) looked for available alternatives for the execution of the activities foreseen (ie. Online surveys). The new company will be in charge of all the pending upgrades and improvements of the website in the next period of ERN-EuroBloodNet implementation.

Explanations for tasks not fully implemented, critical objectives not fully achieved and/or not being on schedule. Explain also the impact on other tasks on the available resources and the planning

As commented in the previous section, the problems faced with the website developers have led to a delay in the implementation of the foreseen activities linked, ie. the publication of the inventory of the guidelines and recommendations or the repository of educational material.

Nevertheless, coordination team put into place available alternatives for the deployment of the actions foreseen in duly time, as the conduction of the online questionnaires for BMT and NGS on non-oncological disorders through google drive.

The new company will start working in the third year of the network implementation and will be in charge of the upgrades of the inventory, as well as of the redesign of the website, including the implementation of new dedicated sections.

1.10. Reasons for deviations from Annex 1

1.10.1. Implementation related deviations

- Explain the reasons for deviations from Annex 1, the consequences and the proposed corrective actions

As previously commented, apart from the delays in the actions concerning the website, we can say that we have followed the working plan and fulfilled most of the tasks and activities defined for this period.

The detailed tasks not fully implemented are detailed in section below.

- Explain **tasks not fully implemented**, critical objectives not fully achieved and/or not being on schedule. Explain also the impact on other tasks on the available resources and the planning.

Based on the previous reasons, the following tasks have not been fully implemented. Foreseen actions and justifications are included:

Task 1.1. Mapping of services (clinical and diagnosis) available in Europe for best clinical care

The survey conducted for establishing the state-of-the-art of PKD in Europe by compiling data on: number of PKD patients, centres performing PK activity and its genetic characterization was foreseen to be expanded to other very rare hematological diseases ie. congenital dyserythropoietic anaemia and hereditary xerocytosis.

Justification: Efforts have been focused on the definition of a second survey for the gathering of more exhaustive data on how expert centers perform PK diagnosis. The survey is being produced based on key indicators extracted from the “Consensus recommendations on the diagnosis of pyruvate kinase deficiency” that may not be widely implemented in the centers performing diagnosis and in collaboration with UKNEQAS. This second exercise will be conducted in the next period of implementation, as well as the translation of the approach followed to other very rare haematological disorders.

Nevertheless, the task is ongoing for the expansion to other very rare disorders and agreements have been reached with members to cover to ultra-rare conditions: a) Rare iron metabolism and b) cutaneous lymphoma. Questionnaires are under development and will be implemented on-line during the 3rd year (new company already identified for programming tasks).

Task 2.3. Foster the creation of new guidelines in collaboration with EHA and their transposition at the national level

A report on guidelines needed to be addressed at the EHA working group was foreseen to be produced based on the gaps identified, sub-thematic areas or specific diseases lacking appropriate guidelines. This task is partially implemented.

Justification: A first analysis of areas where guidelines and recommendations have to be promoted is included in Deliverable 4.1 Report on the comprehensive public database of reliable guidelines. The classification of the documents compiled based on Quality Domains has provided very valuable information on areas remained uncovered by any guidelines or recommendations, or that need to increase the rigour of development based on the evidence.

While the assessment of guidelines and recommendations implementation is ongoing, ERN-EuroBloodNet and EHA maintains a close collaboration for all the activities concerning best practices and especially in the area of guidelines and

recommendations, where TFA coordinators (L Malcovati and A Iolascon) are also representatives at the EHA guidelines working group ensuring the synergies among both groups.

Task 4.2. Constitution of an expert board

A board of experts was foreseen to be constituted for ensuring the coverage of all RHD within the CPMS platform. This task has been partially implemented, as well as their related linked Milestone 17 and 18 Report on Expert Board in CPMS for RHDs (Mo 4 and 12).

Justification: The subnetworks coordinators have provided names for the specific categories of disorders under the subnetwork. These experts have been contacted to invite them to create their profiles at the CPMS, however the board has not been officially constituted since the process for the login experts is still ongoing. The constitution of the expert board is foreseen within the "New task 4.2 ERN-EuroBloodNet strategy for promoting the wide implementation of the CPMS" as a central piece for the CPMS efficiency and will be officially established in the coming period of the network.

Task 5.3. To facilitate the provision of –omics platforms and new technologies

The Milestone 20 Report on OMICS facilities as candidates to participate in the EJP on RDs (Mo 7) has been delayed.

Justification: During this period of implementation other concrete projects have been identified as priorities by the scientific and strategic board, as the definition of educational webinar programs on very concrete needs and gaps identified, or the establishment of the SCD Patients Network as a prevalent disease needed to be empowered not only at the national but European level. Nevertheless, further actions on this task will be implemented in the coming years of network implementation.

ERN-EuroBloodNet Coordination Task 2. Establishment of the Board of National Contact Points (NCPs)

A board of NCPs was foreseen to be established as key actors in the dissemination of ERN-EuroBloodNet activities and results at national level. This task has been delayed, as well as its related linked Milestone 7 Establishment of the Board of National Contact Points (Mo 6).

Justification: There is no doubt that major results from the network are starting to be obtained after this period of implementation. Accordingly the board of NCPs will be implemented during next year, in parallel to all the actions foreseen for the upgrade of the public website, in order to maximize the dissemination and outreach of the outcomes not only at the national but also at the European level.

- Explain **deviations of the use of resources** between actual and planned use of resources in Annex 1 (Description of the Action), especially related to person-months **per work package.**

No major deviations on the use of resources has been produced during this period of implementation.

- Please describe changes to the original planning, their reasoning, which problems occurred and how did you solve them?

Task 3.2. To promote blended educational program (on-site & on-line)

A survey for gathering the already existing e-learning platforms was foreseen to be conducted in order to gather e-learning solutions and make them available linked to

ERN-EuroBloodNet website contributing also to identification of GAPs – Milestone 13 Report on eLearning platforms covering RHDs (Mo 10).

Justification: It was agreed in collaboration with EHA and ESH to analyze the educational gaps through a broader questionnaire aimed to create a comprehensive repository of education materials available for RHD while identifying the educational needs to be addressed in the coming annual work plan with the cooperation of EHA and ESH.

Moreover, in order to promote the blended education on RHD, it was agreed to define the ERN-EuroBloodNet webinars program, with the inclusion of topic specific recorded video sessions provided by experts in the field allow health professionals to learn highly specialized knowledge without the need to travel and whenever they wish. Accordingly, the task 3.2 has been renamed as “New Task 3.2 Webinars program for health professionals”

Task 4.3. Promote CPMS use among members

This task has been undertaken and described within the “New task 4.2 ERN-EuroBloodNet strategy for promoting the wide implementation of the CPMS”

Justification: The strategy for promoting the wide implementation of the CPMS has included during this year two main actions a) the promotion of the use of the CPMS among members and b) upgrade of RHD categories in the “Preferences” section.

1.10.2. Unforeseen subcontracting

Specify in this section:

a) the work (the tasks) performed by a subcontractor which may cover only a limited part of the action

No unforeseen subcontracting has been produced during the second year of the network.

b) Explanation of the circumstances which caused the need for a subcontract, taking into account the specific characteristics of the action

No unforeseen subcontracting has been produced during the second year of the network.

c) the confirmation that the subcontractor has been selected ensuring the best value for money or, if appropriate, the lowest price and avoiding any conflict of interests.

No unforeseen subcontracting has been produced during the second year of the network.

2. FURTHER REMARKS

- Please state further remarks that you find noteworthy

Many activities performed by the ERNs are directly linked to the activities developed by the EC WG on ERNs. Thus, the outcomes of the EC WG activities directly impact on the specific ERN activities. However, participation of an ERN in a given EC WG is not well balanced and the outcomes of each EC WG are not shared with enough time to be analysed by the ERNs not directly involved in order to give appropriate feedback.

An example is the monitoring indicators. The already established set of indicators for monitoring ERNs performance do not reflect many of the activities performed by ERN-EuroBloodNet with relevant impact on the delivery of best care as the result of an European approach (added value) as the establishment of cross border agreements