Deliverable 4
Protocol for creation of the repository of reliable guidelines

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Short description: Protocol for creation of the repository of reliable guidelines including methodology for rating guidelines and prioritization of sub-thematic areas lacking of best quality guidelines.

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1-Background and rationale

1.1 The current situation of Guidelines in the context of Rare Diseases

Clinical practice guidelines are defined as "systematically developed statements to assist practitioners and patient decisions about appropriate health care for specific circumstances". In past decades a great number of guidelines have been produced and implemented supporting the adequate provision of health care for millions of patients across the world. However, when focusing on the health care topics covered, the number of recommendations dedicated to rare diseases (RDs) diminishes dramatically in comparison with the ones addressing common diseases.

In the European Union (EU), a disease is considered as rare when affecting less than 5 per 10,000 persons. Due to their rarity, the development of high quality guidelines for RDs has traditionally been postponed over the years, mostly due to the high development costs for funders who consider more prevalent diseases to be priority investment targets. Fortunately, RD awareness and health related actions have increased in the last few years, including those focused on the development, implementation and dissemination of guidelines and recommendations at European level. The contribution of guidelines to shorten the time to diagnosis and improvement of the quality of care on RDs is now widely acknowledged, and several European countries have included their development as a priority in their respective national plans on RDs.

On the other hand, not only there are few guidelines and recommendations on RDs, but also they are difficult to find. According to a recent ORPHANET publication on guidelines for RDs, (“Clinical Practice Guidelines for Rare Diseases: The Orphanet Database” S.Pavan*et al*.) large national and international databases gathering Clinical Practice Guidelines (CPGs) are available (naming Guidelines International Network (G-I-N), National Guideline Clearing house (NGC),National Institute for Health and Care Excellence (NICE) guidance or Arbeit sgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaftene.V. (AWMF)) but they generally contain very few guidelines specific to RDs, and are difficult to find amongst the mass of recommendations available for more frequent diseases. Moreover, a significant number of the guidelines produced for RDs by research networks, reference centres or other organizations are not published in international peer-reviewed journals, and thus cannot be found in biomedical literature databases. Alternatively, Google searches may help identify RD guidelines, but the specificity of the obtained results is very low.

In addition, there is a trend to produce more recommendations and opinion of experts in detriment of evidence based GPC that of course must be taken into consideration, but not at the same scientific level.

1.2 Guidelines for Rare Hematological Diseases: gaps and needs

A number of CPG have been published on prevention, diagnosis, and clinical care of patients affected by Rare Hematological Diseases (RHDs). Many scientific societies, at the Member State or European level, have produced such guidelines. However, there is no comprehensive repository including quality assessment, gaps identification, level of implementation, updates or any system to guarantee their usefulness and impact in patients' quality of life.

There is a need for harmonised practice and protocols for RHD patients at the European level in order to create equal access to high quality care across the EU. By gathering clinical outcome data on RHD, ERN-EuroBloodNet will be able to promote the development of guidelines to improve clinical knowledge of RHDs. This, in turn, will lead to earlier and better diagnosis, better treatment of patients and contribute to the dissemination of best practices in RHDs.

There are currently many different stages of implementation of guidelines across EU, and one of ERN-EuroBloodNet's main commitments is not only to support guideline development, but also to assess their implementation in the different EU Member States. The last point will also have an impact on national scientific societies and on policy makers in charge of shaping national regulations facilitating guideline implementation in national healthcare systems.

In addition, due to the nature of chronic diseases, multidisciplinary teams have been considered a core model for disease management in this area. The proliferation of multidisciplinary teams in health care has occurred against a background of increasingly specialised medical practice, more complex medical knowledge, continuing clinical uncertainty and the promotion of the patient's role in their own care. In this environment, it is believed that multidisciplinary teams ensure higher-quality decision-making and improved outcomes in the framework of patient pathways. However, the evidence underpinning the development of multidisciplinary teams is not uniform across all RHD areas and the degree to which they have been absorbed into clinical practice varies widely across conditions and EU Member States.

In this context, ERN-EuroBloodNet aims to build and disseminate a comprehensive public database of reliable guidelines for RHD including the impact in patient quality of life through

clinical outcome indicators. Not only will they cover prevention, diagnosis and clinical care of patients, but also the organization of care, in order to provide professionals, patients and policymakers with the highest quality and updated guidance. Moreover, the creation of a comprehensive public database of reliable evidence based guidelines for the organization of patient-centered care in multidisciplinary teams focused on the implementation of clinical pathways for the management of patients affected by a RHD becomes mandatory for an adequate provision of health care to patients across Europe.

Representatives of European Patient Advocacy Groups (ePAGs) play an important role in this regard as they can contribute to defining priorities in guideline production and/or adaptation to different populations as well as implementation and dissemination. The impact of migration in European countries should further also be taken into account when producing, implementing and disseminating guidelines. Cultural as well as socio-economic mediators may be required in migration-prone regions but also in regions with low access to treatment and care.To ensure successful diffusion and implementation, CPG should be framed in ways so as to be applicable in all access contexts prevalent across EU Member States (e.g. including economically affluent as well as less affluent countries).

2- Objectives

ERN-EuroBloodNet established five specific objectives as priorities to be accomplished in the frame of the 5 years of implementation, including the specific objective 2: Promote the best practices in prevention, diagnosis and safe clinical care across Europe.

This objective aims to foster best practice sharing in RHD by creating a comprehensive public database of reliable evidence based guidelines, ranging from prevention, diagnostic tests and treatments to the organisation of patient-centred management in multidisciplinary teams.

The database will serve as a platform for sharing best practices, facilitating timely, effective and efficient translation of research results into patient oriented strategies at the individual and public health levels and provide professionals, patients, and policy makers with the best and most up to date information.

In line with the specific objective 2, two goals were defined to be accomplished in the first year of the ERN:

- Establish a collaboration agreement with the Rare Best Practices project (rbpresearch.eu) to gather existing guidelines in RHD and assess their quality through a systematic methodology based on the GRADE methodology and reporting checklists providing guidance about the essential components of high quality practice guidelines.
- Conduct a survey among ERN-EuroBloodNet members to compile all the guidelines implemented in the different sub-networks

3- Methods

3.1 Transversal Field of Action on Best Practices

The implementation of the ERN-EuroBloodNet action plan has been assured through the establishment of five Transversal Fields of Action (TFAs) in line with each specific objective of the network. In this context, the TFA on Best Practices was established aiming to implement all tasks and activities related to the achievement of the specific objective 2.

At the beginning of the network, it was agreed that every TFA would be coordinated by one representative from the oncological hub, one representative from the non-oncological hub, and one ePAG representative in order to ensure a balanced coordination of the actions performed. The TFA on Best Practices is coordinated by:

- Luca Malcovati, Foundation IRCCS Polyclinic San Matteo, Pavia - Oncological representative: Luca is Associate Professor of Hematology at the University of Pavia & IRCCS Policlinico San Matteo Foundation. He coordinated the development of recommendations for the diagnosis and treatment of myelodysplastic syndromes on behalf of the European LeukemiaNet, and was member of the Steering Committee for recommendations for allogeneic hematopoietic stem cell transplantation for myelodysplastic syndromes and chronic myelomonocutic leukemia. He is currently Chair of the Working Group of the European Hematology Association for the development of recommendations in hematologic diseases.

- Achille Iolascon, AOU Federico II, Naples – Non oncological representative: Achille is a Professor of paediatrics since 1994 and a Professor of medical genetics since 2004. He is the chairman of Medical Genetics at AOU University Federico II of Naples (Italy). His main area of expertise is red cell membrane disorders and erythropoiesis and the main achievements in the field of best practices were related to studies on hereditary spherocytosis and ellyptocytosis. He has also performed activities related to mapping and cloning of several genes such as: hereditary thrombocytopenia, congenital dyserythropoietic anemia type I and type II, DMT1 deficiency in humans, hereditary stomatocytosis (DHS) and familial pseudohyperkalemia. His research group is particularly interested in spread the knowledge on rare anemias and red cell biology.

- Amanda Bok, European Haemophilia Consortium - ePAG representative: Amanda is CEO of the European Haemophilia Consortium and brings community experience liaising and co-producing consensus statements/recommendations in multidisciplinary groups containing patients, multidisciplinary teams of health care providersand regulators.

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

In the context of the TFA on Best Practices, the creation of a comprehensive public database of reliable guidelines, ranging from prevention, diagnostic tests and treatments to the organisation of patient-centred care in multidisciplinary teams and patient safety was foreseen for the first year of implementation of the network. For this aim, the following subtasks were foreseen under the 1st year Action Plan:

Task 1. Collaboration agreement with Rare Best Practice project

A collaboration agreement was foreseen to be established with Rare Best Practice project (rbpresearch.eu), in order to gather existing guidelines for RHD and evaluate their level of fulfillment with quality standards based on the GRADE methodology.

Task2. Questionnaire conducted among ERN-EuroBloodNet members

A survey was foreseen to be conducted in parallel to task 1 among ERN-EuroBloodNet members according to their participation in the six sub-thematic areas. This survey should be designed to gather valuable information to assess the level of awareness, implementation and assessment through clinical outcome indicators, of existing guidelines.

Task 3. Protocol for the creation of the repository of reliable guidelines

Finally, a protocol for the creation of the repository of reliable guidelines including the methodology for rating guidelines and prioritization of sub-thematic areas lacking best quality guidelines was foreseen to be elaborated and to be submitted to the European Hematology Association (EHA) working group on guidelines.

3.2.1 Modifications on the action plan

During the first year, the TFA on Best Practices has focused on the gathering of guidelines and recommendations available for RHD. The methodology for this aim has been established in order to get useful outcomes for the assessment of the guidelines to be performed within the second year of the network.

Based on face to face meetings and teleconference discussions, and taking into consideration the input from the RD-ACTION & DG Sante Workshop: “How can ERNs generate, appraise and utilise clinical practice guidelines, to enhance the impact and deployment of consensus guidelines in national health systems?”, the following modification on the action plan was performed:

Task2. Questionnaire conducted among ERN-EuroBloodNet members

After an analysis undertaken by the ERN-EuroBloodNet coordination team, a common need across all TFAs was identified regarding the need for the gathering of available services/activities/resources within the network. In order to address this need, a transversal methodology was defined by the coordination team including a set of online questionnaires to be conducted among ERN-EuroBloodNet members encompassing the different key items of each of the TFAs.

TFA targeted online questionnaires were agreed to be endorsed in ERN-EuroBloodNet website in order to facilitate the gathering of answers from the members and their analysis. As a result, all the different gaps within the TFAs will be identified and planned to be addressed in the coming annual work plans.

In order to get the maximum number of answers from the experts on RHD, the launch of TFAs questionnaires was agreed to be performed once the inventory of ERN-EuroBloodNet members and experts was finalized.

The questionnaire for the TFA on Best Practices was discussed during the Teleconferences among the TFA coordinators and coordination team, as well as during the Scientific and Strategic Board Meetings.

The final questionnaire was agreed and included in the protocol for creation of the repository of reliable guidelines as a complementary action needed for the target objective.

3.3 Activities implemented in the first year of ERN-EuroBloodNet

3.3.1 Collaboration agreement with Rare Best Practice project

One of the main objectives of Rare Best Practice project is to build a comprehensive public database of trustworthy guidelines, ranging from diagnostic tests and treatments to the

organization of care, to help professionals, patients, policy makers with the best and most up to date information on Rare Diseases.

In line with this objective, a collaboration agreement will be reached among Rare Best Practice coordinator, Domenica Taruscio, and ERN-EuroBloodNet to joint efforts in towards this common goal, enhancing the outcomes and avoiding overlapping of tasks.

3.3.2 Protocol for the creation of the repository of reliable guidelines

The protocol established for the creation of the repository of reliable guidelines on RHD is based in two complimentary approaches:

a) Creation of a list of international guidelines

A list of international guidelines has been created with the input of ERN-EuroBloodNet subnetworks coordinators with the aim to compile the most frequent guidelines used for the main RHD conditions. This list represents the starting point for the gathering of the most implemented guidelines at European and International levels.

A common methodology for the type of information to be gathered was established, including:

1) Diseases covered by the guideline
2) Title of the guideline
3) Link or PDF to access the guideline

Given the expertise of the subnetworks coordinators, the coverage of the list is well balanced through the different RHDs. The list is available in Annex I List of international guidelines.

b) Questionnaire conducted among ERN-EuroBloodNet members

Following the methodology established for the other TFAs, an online questionnaire will be loaded on to the ERN-EuroBloodNet website in order to gather key essential information from the members regarding existing activities/services/initiatives related to guidelines and best practices (Annex II Online questionnaire on existing guidelines).

The questionnaire will show the list of international guidelines in order to be able to be selected if they are implemented in the healthcare providers.

In those cases where members follow different guidelines from the ones including in the list, they will be able to include the information related to the guidelines implemented in their healthcare providers.

In result, the online questionnaire will provide with the information on the guidelines implemented a) for the coverage of very rare diseases or b) at national level, complementing the list of international guidelines.

4-Expected outcomes and next steps

4.1. Expected outcomes

The protocol for the creation of the repository of reliable guidelines on RHD has been designed allowing the identification of a wide variety of guidelines through two different approaches:

- Identification of the most common used guidelines at EU and international level for the most frequent RHD – List of international guidelines
- Identification of the guidelines used for the less prevalent RHD (including very rare diseases) and national guidelines – Online questionnaire to ERN-EuroBloodNet members

As a result, the implementation of the protocol will lead to an accurate and reliable source of information on the guidelines followed by the ERN-EuroBloodNet members that will allow the identification of valuable gaps at each Member State and EU level to be addressed in the coming years. In turn, this will promote the delivery of highly specialised procedures and treatments and the harmonisation of care delivery across the EU.

In addition, as one of the centrepiece of the protocol, the questionnaire has been designed to gather essential information related to their real implementation at the healthcare provider as well as personal comments that will be deeply analyzed for the production of outcomes, not only at the theoretical level, but also in the practical one.

In addition, in general terms and based on the gaps that will be identified, ERN-EuroBloodNet TFA on Best Practices is expected to achieve the following outcomes and impact:

- Research recommendations: they arise from translating gaps or uncertainties in the evidence base into specific statements valuable to prioritise research efforts and resources.
- Allocation of resources: Assessment of the level of implementation of guidelines will aid in defining priority services and promote their delivery at the European or EU Member State level.
- Training recommendations: in sub-thematic areas where guidelines are rated with a low score regarding their implementation level, training activities will be recommended for targeting key stakeholders to spread expertise and knowledge in the field of guidelines.

4.2 Target groups

Both non-experts and experts in RHD will 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 the EU. The expected target audiences that will directly benefit from the specific outcomes include:

- Health care professionals who are not experts in RHD and in need of guidance for daily patient clinical care.
- Patients and patient organisations able to directly and indirectly advocate for adequate patient treatment and care.
- National health authorities responsible for health policies for the implementation of guidelines.
- National societies in charge of producing national guidelines and/or implementing European/International ones.

4.3 Dissemination

In order to increase as much as possible the diffusion and implementation of existing reliable guidelines, the following channels will be employed:

- The database of reliable evidence based guidelines will be made accessible through ERN-EuroBloodNet, as well as the annual reports for guideline implementation and patient safety standards and measures.
- Existing guidelines with poor implementation will be disseminated through the different educational systems to increase their awareness and use, e.g.: European symposia and training courses.
- Short stays of health care professionals will strengthen professional relations and facilitate the adoption of a position paper for the prioritization of development of guidelines and monitor the level of implementation of existing ones and the differences across EU.
- ePAGs-led surveys among patients to collect their expectations on Centers of Expertise and input on the guidelines implementation.

4.4 Next steps

The protocol for the creation of the repository of reliable guidelines described in this report will be implemented in the next stage of development of the ERN-EuroBloodNet.

The list of international guidelines produced will be implemented in the back office of the website in order to provide experts fulfilling the online questionnaire the possibility of selecting those guidelines implemented in their healthcare providers, while if different ones are followed, they will be able to include the information related to the guidelines implemented. In result, the online questionnaire will provide with the information on the guidelines implemented a) for the coverage of very rare diseases or b) at national level, complementing the list of international guidelines.

In addition, once the full database is created, guidelines gathered will be evaluated through quality standards based on GRADE/AGREE II methodology, providing a comprehensive public database of reliable guidelines that will be available at ERN-EuroBloodNet website and that will serve as starting point for two fundamental pillars in the coming periods of the ERN-EuroBloodNet:

- Assess the level of awareness and implementation of existing guidelines among ERN-EuroBloodNet members
- Foster the creation of new guidelines and their transposition at the national level based on the gaps identified

Annex I

List of international guidelines

Guidelines			Myeloid malignancies									Comments
nº	Title of the guideline	Link	Myelodysplastic syndrome (MDS)	Acute myeloid leukemia (AML)	Chronic myelomonocytic leukemia (CMML)	Chronic Myeloid Leukemia (CML)	Myeloproliferative neoplasm (MPN)	Myelofibrosis	Systemic mastocytosis	Histiocytosis	Other disease/group of diseases	
1	(German guideline)	https://www.onkopedia.com/de/onkopedia/guidelines	x	x	x	x	x	x	x	x		
2	Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet	http://www.bloodjournal.org/content/122/17/2943?sso-checked=true	x									
3	Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel.	https://www.ncbi.nlm.nih.gov/pubmed?term=27895058		x								
4	NCCN Guidelines Insights: Myeloproliferative Neoplasms, Version 2.2018.	https://www.ncbi.nlm.nih.gov/pubmed/28982745					x					
5	Evolving concepts in the management of chronic myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet	http://www.bloodjournal.org/content/108/6/1809?sso-checked=true				x						
6	Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet	http://www.bloodjournal.org/content/113/9/1875									x	Acute promyelocytic leukemia
7	Diagnosis and management of mastocytosis: an emerging challenge in applied hematology	https://www.ncbi.nlm.nih.gov/pubmed/26637707							x			

Guidelines			Lymphoid malignancies			
nº	Title of the guideline	Link	Acute lymphoblastic leukemia (ALL)	Marginal zone lymphomas	Light chain Amyloidosis (AL amyloidosis)	Other disease/group of diseases
1	ESMO Guidelines consensus conference on malignant lymphoma 2011 part 1: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL)	https://www.ncbi.nlm.nih.gov/pubmed/23175624				
2	ESMO Consensus conferences: guidelines on malignant lymphoma. part 2: marginal zone lymphoma, malignant lymphoma. part 2: marginal zone lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma	https://www.ncbi.nlm.nih.gov/pubmed/?term=ESMO+Consensus+conferences%3A+guidelines+on+malignant+lymphoma+part+2		x		
3	Hairy cell leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	https://academic.oup.com/annonc/article/26/suppl_5/v100/343998		x		
4	AL amyloidosis: from molecular mechanisms to targeted therapies	http://asheducationbook.hematologylibrary.org/content/2017/1/1.abstract			x	
5	Update on nodal and splenic marginal zone lymphoma	http://asheducationbook.hematologylibrary.org/content/2017/1/371.abstract		x		
6	Acute lymphoblastic leukemia in adult patients: ESMO clinical practice guidelines for diagnosis, treatment and follow-up	https://academic.oup.com/annonc/article/27/suppl_5/v69/1741378	x			
7	Acute lymphoblastic leukemia: Version 2.2015	https://www.ncbi.nlm.nih.gov/pubmed/26483064	x			
8	Gastric marginal zone lymphoam of MALT type: ESMO clinical practice guidelines for diagnosis, treatment and follow-up	https://academic.oup.com/annonc/article/24/suppl_6/vi144/161166		x		
9	Guidelines on the management of AL amyloidosis	http://onlinelibrary.wiley.com/doi/10.1111/bjh.13155/abstract;jsessionid=1626E483AF75599502BC905EAA708327.f01t03			x	
10	Hodgkin´s lymphoma: ESMO clinical practice guidelines on diagnosis, treatment and management	https://academic.oup.com/annonc/article/25/suppl_3/iii70/1741087				x
11	Hodgkin lymphoma, Version 1.2017	https://www.ncbi.nlm.nih.gov/pubmed/28476741				x
12	Hodgkin´s lymphoma in adults: diagnosis, treatment and follow-up	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3608228/				x

Guidelines			Rare Red blood cell defects				
nº	**Title of the guideline**	**Link**	**Haemoglobinopathy**	**Hereditary erythroenzymopathies**	**Hereditary RBC membrane defects**	**Congenital Erythrocytosis**	**Other disease/group of diseases**
1	Guidelines for the diagnosis and management of hereditary spherocytosis – 2011 update	https://www.ncbi.nlm.nih.gov/pubmed/22055020			x		
2	ICSH guidelines for the laboratory diagnosis of nonimmune hereditary red cell membrane disorders	https://www.ncbi.nlm.nih.gov/pubmed/25790109			x		
3	Standards for the clinical care of children and adults with thalassaemia in the UK	http://ukts.org/standards/Standards-2016final.pdf	x				
4	Recommendations regarding splenectomy in hereditary hemolytic anemias.	http://www.haematologica.org/content/102/8/1304	x	x	x		x
5	Management of Non-Transfusion-Dependent Thalassemia: A Practical Guide	https://www.ncbi.nlm.nih.gov/pubmed/25255924	x				
6	EMQN Best Practice Guidelines for molecular and haematology methods for carrier identification and prenatal diagnosis of the haemoglobinopathies	https://www.ncbi.nlm.nih.gov/pubmed/25052315	x				
7	Significant haemoglobinopathies: guidelines for screening and diagnosis	http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2009.08054.x/abstract	x				
8	NHS SCT Handbook for Newborn Laboratories	https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/656094/Antenatal_Laboratory_Handbook.pdf	x				
9	Antenatal Laboratory Handbook SCD Thal	https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/585126/NHS_SCT_Handbook_for_Newborn_Laboratories.pdf	x				
10	The management of SCD	https://www.nhlbi.nih.gov/files/docs/guidelines/sc_mngt.pdf	x				
11	ENERCA clinical recommendations for disease management and prevention of complications of sickle cell disease in children	https://www.ncbi.nlm.nih.gov/pubmed/20981677					
	TIF PUBLICATIONS AND GUIDELINES	http://thalassaemia.org.cy/publications/tif-publications/					
12	Prevention and Diagnosis of Haemoglobinopathies: A Short Guide for Health Professionals and Laboratory Scientists (2016)	http://thalassaemia.org.cy/publications/tif-publications/prevention-and-diagnosis-of-haemoglobinopathies-a-short-guide-for-health-professionals-and-laboratory-scientists/	x				
13	Guidelines for the management of non transfusion dependent thalassaemia (NTDT) 2ND edition	http://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-clinical-management-of-non-transfusion-dependent-thalassaemias-updated-version/	x				
14	A guide for haemoglobinopathy nurse	http://thalassaemia.org.cy/publications/tif-publications/a-guide-for-the-haemoglobinopathy-nurse-2013/	x				
15	Prevention of Thalassaemias and other Haemoglobin Disorders, Vol 1, 2nd Edition (2013)	http://thalassaemia.org.cy/publications/tif-publications/prevention-of-thalassaemias-and-other-haemoglobin-disorders-vol-1-2nd-edition-2013/	x				
16	A Short Guide to the Management of Transfusion Dependent Thalassaemia	http://thalassaemia.org.cy/publications/tif-publications/a-short-guide-to-the-management-of-transfusion-dependent-thalassaemia/	x				
17	Emergency Management of Thalassaemia (2012)	http://thalassaemia.org.cy/publications/tif-publications/emergency-management-of-thalassaemia-2012/	x				
18	Guidelines for the Management of Transfusion Dependent Thalassaemia, 3rd Edition (2014)	http://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-transfusion-dependent-thalassaemia-3rd-edition-2014/	x				
19	Prevention of Thalassaemias and Other Haemoglobin Disorders, Vol. 2: Laboratory Protocols (2012)	http://thalassaemia.org.cy/publications/tif-publications/prevention-of-thalassaemias-and-other-haemoglobin-disorders-vol-2-laboratory-protocols-2012/	x				
20	Guidelines for the Management of Transfusion Dependent Thalassaemia, 3rd Edition (2014)	http://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-transfusion-dependent-thalassaemia-3rd-edition-2014/	x				

Guidelines			Bone marrow failure (BMF) and rare haematopoietic disorders					Comments
nº	Title of the guideline	Link	Congenital dyserythropoietic anemia	Blackfan-Diamond anemia	BMF- Acquired (Aplastic Anaemia and Paroxysmal Nocturnal Hemoglobinuria)	BMF Inherited (Fanconi anemia, Dyskeratosis congenital, GATA2 syndrome,Congenital amegakaryocytic thrombocytopenia and others)	Other disease/group of diseases	
1	Diagnosis and management of congenital dyserythropoietic anemias	https://www.ncbi.nlm.nih.gov/pubmed/26653117	x					
2	Diagnosing and treating Diamond Blackfan anaemia: results of an international clinical consensus conference	https://www.ncbi.nlm.nih.gov/pubmed/18671700		x				
3	How I treat Diamond-Blackfan anemia	http://www.bloodjournal.org/content/116/19/3715?sso-checked=true		x				
4	Transient erythroblastopenia of childhood is an underdiagnosed and self-limiting disease	https://www.ncbi.nlm.nih.gov/pubmed/24635829					x	Transient erythroblastopenia of childhood
5	Guidelines for the diagnosis and management of adult aplastic anaemia	https://www.ncbi.nlm.nih.gov/pubmed/26568159			x			Adult aplastic anaemia
6	How I manage patients with Fanconi anaemia	https://www.ncbi.nlm.nih.gov/pubmed/28474441				x		Guidelines before clonal evolutionAnemia de Fanconi - Dufour
7	How I treat MDS and AML in Fanconi anemia	http://www.bloodjournal.org/content/127/24/2971				x	x	Fanconi+MDS+AML
8	Paroxysmal nocturnal hemoglobinuria	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4215311/			x			
9	Paroxysmal Nocturnal Hemoglobinuria	https://www.intechopen.com/books/anemia/paroxysmal-nocturnal-hemoglobinuria" title="Paroxysmal Nocturnal Hemoglobinuria">Paroxysmal Nocturnal Hemoglobinuria			x			
10	Haematopoietic and immune defects associated with GATA2 mutation	https://www.ncbi.nlm.nih.gov/pubmed/25707267				x		
11	GATA2deficiency andrelatedmyeloidneoplasms	https://www.sciencedirect.com/science/article/pii/S0037196317300604				x		
12	Transplantation for bone marrow failure: current issues	https://www.ncbi.nlm.nih.gov/pubmed/27913467					x	BMT in those BMF conditions inherited or acquired
13	Recommendations on hematopoietic stem cell transplantation for inherited bone marrow failure syndromes	https://www.ncbi.nlm.nih.gov/pubmed/26052913					x	BMT in those BMF conditions inherited or acquired

Guidelines			Rare bleeding-coagulation disorders				
nº	Title of the guideline	Link	Haemophilia A and B (including female carriers)	The rarer congenital deficiencies of other coagulation factors (such as fibrinogen and factors II, V, VII, X, XI and XIII)	Von Willebrand disease	Inherited platelet defects.	Other disease/group of diseases
1	WFH Guidelines: Guidelines for the management of haemophilia	http://www.haemophiliacentral.org/Guidelines.aspx	x				
2	Guideline on the management of haemophilia in the fetus and neonate	http://www.haemophiliacentral.org/Guidelines.aspx	x				
3	Practice Guidelines for the Molecular Diagnosis of Haemophilia A	http://www.haemophiliacentral.org/Guidelines.aspx	x				
4	Practice Guidelines for the Molecular Diagnosis of Haemophilia B	http://www.haemophiliacentral.org/Guidelines.aspx	x				
5	A United Kingdom Haemophilia Centre Doctors' Organization guideline approved by the British Committee for Standards in Haematology: guideline on the use of prophylactic factor VIII concentrate in children and adults with severe haemophilia A	http://www.haemophiliacentral.org/Guidelines.aspx	x				
6	Guideline on the selection and use of therapeutic products to treat haemophilia and other hereditary bleeding disorders. A United Kingdom Haemophilia Center Doctors' Organisation (UKHCDO) guideline approved by the British Committee for Standards in Haematology	http://www.haemophiliacentral.org/Guidelines.aspx	x				
7	A review of inherited platelet disorders with guidelines for their management on behalf of the UKHCDO	http://www.haemophiliacentral.org/Guidelines.aspx				x	
8	The molecular analysis of von Willebrand disease: a guideline from the UK Haemophilia Centre Doctors' Organisation Haemophilia Genetics Laboratory Network	http://www.haemophiliacentral.org/Guidelines.aspx			x		
9	Management of von Willebrand's disease: a guideline from the UK Haemophilia Centre Doctors' Organisation	http://www.haemophiliacentral.org/Guidelines.aspx			x		
10	The diagnosis of von Willebrand's disease: a guideline from the UK Haemophilia Centre Doctors' Organisation	http://www.haemophiliacentral.org/Guidelines.aspx			x		

Guidelines			Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis					Comments
nº	Title of the guideline	Link	non-HFE related hereditary hemochromatosis: (HH types 2A, 2B, 3 and 4A,4B), TFH1-Related Hemochromatosis (type V), Hereditary Hyperferritinemia Cataract Syndrome (HHCS)	HFE-related hereditary hemochromatosis with established severe clinical expression or due to very rare mutations in HFE	Low iron availability for erythropoiesis: Iron Refractory Iron deficiency Anemia (IRIDA), Aceruloplasminemia (ACP)	Rare defects in iron acquisition and transport: Atransferrinemia, Microcytic anemia with iron loading (DMT1), Sideroblastic anemia (STEAP3)	Defects in heme synthesis or Fe-S cluster biogenesis: Sideroblastic anemias (SLC25A38, GLRX5; HSPA9), XLSA with ataxia (ABCB7), XLSA (ALAS2)	
1	The quality of hereditary haemochromatosis guidelines: a comparative analysis	https://www.ncbi.nlm.nih.gov/pubmed/25441394		x				Important as a tool to question the need for more extended evidence
2	European Association For The Study Of The Liver. EASL clinical practice guidelines for HFE hemochromatosis.	https://www.ncbi.nlm.nih.gov/pubmed/20471131		x				Used in practice by most people; very good GL; may require updating (extend information on utilization of quantitative MRI, elastometry, introduce Gaucher disease as case of hyperferritinemia with normal TS, usefulness of family history for evaluation of hyperferritinemia (early cataract) and oculistic evaluation before performing MRI). It does not include non-HFE HH.
3	American Association for the Study of Liver Diseases.Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases	https://www.ncbi.nlm.nih.gov/pubmed/21452290		x				Some divergences with the European guidelines (namely on the value of the H63D variant). There are some limits: better define the role of compound heterozygosity and H63D homozygosity; better define cut off for alcohol intake (>60g/day seems too high); there is no mention of quantitative MRI for assessing iron overload and of elastometry to assess fibrosis; concern about the limitation of using vitamin C during phlebotomies (refers to a single report in 2 thalassemia major patient with marked iron overload); concern about the indication of regular phlebotomies in patients with end-organ damage (should iron chelation be recommend and/or erythrocytapheresis).
4	EMQN best practice guidelines for the molecular genetic diagnosis of hereditary hemochromatosis (HH)	https://www.ncbi.nlm.nih.gov/pubmed/26153218		x				The most updated guidelines on genetic testing. Few points may need to be rediscussed or extended e.g. the concept that patients with compound heterozygosity for p.C282Y and another rare mutation or those with HFE deletion should be included in a separate group of rare hereditary HH, not all experts agree, and believe they belong to HFE-HH); the paper is mainly devoted to diagnosis of HFE related HH and there is only a small parto n non-HFE.
5	Reassessing the Safety Concerns of Utilizing Blood Donations from Patients with Hemochromatosis. Hepatology	https://www.ncbi.nlm.nih.gov/pubmed/28902419		x				These are not guidelines but important as recommendation
6	Molecular diagnosis of hemochromatosis	https://www.ncbi.nlm.nih.gov/pubmed/23530886	x					Expert opinion" based recommendations and "in house recommendations"
7	Practice guidelines for the diagnosis and management of microcytic anemias due to genetic disorders of iron metabolism or heme synthesis	https://www.ncbi.nlm.nih.gov/pubmed/24665134			x	x	x	Only guideline available on this topic. It does not cover SA due to HSPA9-variants since this latter disorder is described after the publication of the guidelines

Annex II

Online questionnaire on existing guidelines

Respondent's Data

1) Name and surname
2) E-mail
3) Phone
4) If you are a Health professional whose centre is a member of ERN-EuroBloodNet, select it from the following list:

To be selected from the list of the 66 centres

5) If you are a Health professional whose centre is NOT member of ERN-EuroBloodNet, complete the following data:

- Name of your Centre
- City
- Country

6) If you answering as a representative of a National Society, complete the following data:

- Name of the National Society:

"Guideline/Recommendation" Information

Do you follow some of the international guidelines included in this list?

List of international guidelines

If you do not follow any from the list or have implemented different one/s, please complete the following information:

7) Title:
8) Available at (eg. Link if available on-line, reference if published…):
9) Year of publication:
10) Languages in which the "Guideline/Recommendation" is available:
11) Geographic area covered by the "Guideline/Recommendation"

- National
- Regional

- European
- International

12) To which "Disease/group of diseases" does the "Guideline/Recommendation" apply?

13) Which category does this group of "Disease/group of diseases" belong to?

- Myeloid malignancies
- Lymphoid malignancies
- Rare red blood cell defects
- Bone marrow failure and rare haematopoietic disorders
- Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis
- Rare bleeding-coagulation disorders

14) Which areas of treatment and care are covered by the "Guideline/Recommendation"?

- Diagnosis
- Prevention
- Therapy

15) Specify the health care service covered by the "Guideline/Recommendation" (e.g. SCT, molecular diagnosis, splenectomy, neonatal screening):

16) What is the population scope of the "Guideline/Recommendation"?

- Neonatal
- Paediatric
- Transition from pediatrics to adulthood
- Adulthood
- Pregnancy
- Elderly/Ageing

17) Is the "Guideline/Recommendation" followed in your Centre?

- Yes
- No
- Partially

If you answered "No" or "Partially" specify the main reasons for non use of the "Guideline/Recommendation" (e.g. lack of a procedure, lack of treatment product availability, etc.)

If you answered "Yes" or "Partially", are there clinical outcome indicators in place for assessment?

- Yes
- No

18) Do you have any personal comments on the "Guideline/Recommendation" (e.g. need to be updated, difficult to be implemented, need to be adapted to population groups, etc.)

Insert another "Guideline/Recommendation" Finish