

DELIVERABLE 5.3 ERN-EUROBLOODNET REPOSITORY OF CLINICAL PRACTICE GUIDELINES AND OTHER CLINICAL DECISION MAKING TOOLS ON RHD 3

ERN-EuroBloodNet: European Reference Network on Rare Hematological Diseases

EUROPEAN REFERENCE NETWORKS
FOR RARE, LOW PREVALENCE AND COMPLEX DISEASES

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Short Description

Report on the comprehensive public database of reliable clinical practice guidelines and other clinical decision making tools and actions for promoting the creation of new best practice documents.

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1. INTRODUCTION

CLINICAL PRACTICE GUIDELINES AND OTHER CLINICAL DECISION MAKING TOOLS FOR RARE HEMATOLOGICAL DISEASES, GAPS AND NEEDS

Clinical decision support systems represent nowadays essential tools for health professionals to guide on the next steps to take on the prevention, diagnosis, treatment and management of patients, considering the latest information and data available on the field and aiming to deliver value-based health care.

In the area of clinical decision support systems, different types of tools are identified based on the procedure followed for its development. As defined by the ERN Continuous Monitoring Working Group of the Member States and the ERN Coordinators, Clinical practice guidelines (CPGs) are defined as "statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options". While on the other hand, other Clinical Decision Making Tools (CDMTs) "Clinical Consensus Statement is the end product developed by an independent panel of (at least 3) subject matter experts convened specifically to perform a systematic review of the available literature, for the purpose of understanding a clinically relevant issue or surgical procedure, offering specific recommendations on a topic. Compared to Clinical Practice Guidelines and Clinical Practice Recommendations, Clinical Consensus Statements undergo a less rigorous peer review process."

In this context, during past decades a great number of clinical decision support systems have been produced and implemented supporting the adequate provision of health care for millions of patients across the world. However, due to the low prevalence of Rare Diseases (RD), the development of high quality guidelines has usually been postponed for the prioritization of more prevalent diseases. Fortunately, the contribution of these support tools to shorten the time to diagnosis and improvement of the quality of care on RDs is now widely acknowledged, and several European countries have recently included their development as a priority in their national plans on RDs.

Another issue is the lack of findability of CPG and CDMT tackling RDs. According to "Clinical Practice Guidelines for Rare Diseases: The Orphanet Database", there are a large number of national and international databases gathering CPGs, but generally containing very few addressing 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.

As for other RDs, this scenario remains when focusing on Rare hematological diseases (RHDs). A number of CPGs and CDMTs have been published on prevention, diagnosis, and clinical care of patients and many scientific societies have produced such guidelines at the national or European level. However there is no repository including quality assessment, evaluation of gaps or level of implementation, updates or any system to guarantee their usefulness and impact in patients' quality of life.

Accordingly, ERN-EuroBloodNet identified as a high priority to generate a comprehensive repository of CPG and CDMTs and the definition of a methodology for their classification based on quality domains and assessment of real translation into clinical practice with the final aim to, not only support guideline development when lacking, but also assess their implementation in the different EU Member States.

ERN-EUROBLOODNET REPOSITORY OF CPGs AND OTHER CDMTs

List of international CPGs and other CDMTs

In the first two years of ERN-EuroBloodNet implementation (2017-2018), a protocol for the creation of the repository of CPGs and other CDMTs on RHD was defined aiming to achieve an accurate and reliable source of information on the guidelines and recommendations followed by the ERN-EuroBloodNet members. A first list of 69 CPGs and other CDMTs on RHD was identified with the feedback from subnetworks coordinators and members.

This first list 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. [Final list included a total of 116 CPGs and other CDMTs.](#)

Classification based on Quality domains

A methodology for classification of CPGs and other CDMTs based on Quality Domains was defined according to three domains: Scope and purpose, patients involvement and rigour of development.

As result for the classification exercise, a total of 68 CPGs and other CDMTs were classified with the participation of 10 ERN-EuroBloodNet experts as follows: 24 for Red blood cell disorders, 13 for Bone marrow failures, 6 for Haemochromatosis and other iron related disorders, 26 for Myeloid diseases (The task is still ongoing for the Bleeding and coagulation disorders and Lymphoid malignancies.)

In addition, the [search engine](#) implemented allows the findability of the CPGs and other CDMTs classified on quality domains, promoting the searchability by concrete needs of the RHD community, including: subnetwork, RHDs Disease Groups, Scope and Purpose (Prevention, Diagnosis, Treatment, and Rigour of development), or Rigour of Development (A Evidence and consensus based, B Consensus based, C Expert opinion).

Full details of the classification and creation of search tool is available at "Deliverable 5.2 ERN-EuroBloodNet repository of clinical practice guidelines and other clinical decision making tools on RHD" (February 2021).

DG SANTE ACTION FOR SUPPORTING ERNs ON CPGs AND OTHER CDMTs

ERN-EuroBloodNet is one of the members of the "ERN Working Group on Knowledge Generation", with the representation of Luca Malcovati, ERN-EuroBloodNet representative for best practices and chair of EHA Working group on guidelines, and Maria del Mar Mañú Pereira, ERN-EuroBloodNet scientific director. The working group has 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.

DG SANTE is supporting ERNs on the development of CPGs and other CDMTs for rare diseases. In this sense, the ERN Guidelines project (Tender N° SANTE(2018/B3/030) aims to provide a common methodology, in order to harmonise the elaboration process of CPGs and CDSTs in the ERNs.

The tender aims to develop *de novo* or appraise/adapt 2 new CPGs and 5 CDMTs per ERN according to the request and need of the ERNs. Tender includes the support with the provision of human and technical resources. In addition, a training program will be offered to educate 1 representative per network as expert in the field, and 5 representatives per network as intermediate experts.

In order to identify the needs for each ERNs to for the development/appraise of CPGs and other CDMTs, a first round of consultation process was conducted by the contractors, aiming to identify diseases or conditions that most urgently require evidence-based CPGs/CDMTs to ensure the highest standards of quality care. For the identification of the ERN-EuroBloodNet top 10 priorities, a survey was circulated among ERN-EuroBloodNet members for the provision of the gaps for each disease/condition they considered there is a need for CPGs/CDSTs development/adaptation.

As a result from the survey, the Top 10 priority list for CPGs and other CDMTs development identified by ERN-EuroBloodNet allowed the targeting of the most important areas to be tackled in the next steps on the EC tender for the development of 2 new CPGs and 5 new CDMTs. Survey and Top 10 list can be found at "Deliverable 5.2 ERN-EuroBloodNet repository of clinical practice guidelines and other clinical decision making tools on RHD" (February 2021)."

COLLABORATION WITH THE EUROPEAN HEMATOLOGY ASSOCIATION (EHA)

The [European Hematology Association](#) (EHA) is a non-profit association that promotes excellence in patient care, research and education in hematology by organizing an annual congress, providing an educational program based on the European Hematology Curriculum, publishing a journal, lobbying for hematology and promoting research. The association supports hematologists in and outside Europe to further improve hematology patient care;

A collaboration with the EHA Guidelines Committee has been established aiming to promote and support the creation and adoption of guidelines for diagnosis and treatment of hematologic diseases.

2. OBJECTIVES

One of the key objectives established by ERN-EuroBloodNet is to foster best practice sharing in RHD by creating a comprehensive public repository of reliable evidence based CPGs and other CDMTs, ranging from prevention, diagnostic tests and treatments to the organisation of patient-centred management in multidisciplinary teams.

The repository of guidelines and recommendations will serve as a central 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.

Based on the actions presented at the "Deliverable 5.2 ERN-EuroBloodNet repository of clinical practice guidelines and other clinical decision making tools on RHD 2" (February 2021), this Deliverable presents the actions undertaken to:

- a) Creation of a CPG on Adult Burkitt Lymphoma in the frame of DG SANTE supporting action
- b) Creation of Recommendations for diagnosis and treatment of methemoglobinemia in the frame of the collaboration with the European Hematology Association (EHA)

3. ACTIONS

CLINICAL PRACTICE GUIDELINE ON ADULT BURKITT LYMPHOMA

Based on the ERN-EuroBloodNet Top 10 list for CPGs and other CDMTs priorities development, the first topic selected to be developed under the frame of DG SANTE supporting action was the creation of the Clinical Practice Guideline for Adult Burkitt Lymphoma, as a very rare lymphoma requiring from very concrete expertise for the proper diagnosis, prognosis and treatment, and lacking from clinical practice guidelines to date.

In the context of ERN Guidelines project (Tender N° SANTE(2018/B3/030) supporting ERNs in the elaboration process of CPGs and CDSTs, the member of the Consortium assigned to ERN-EuroBloodNet was "Servicio de Evaluación del Servicio Canario de la Salud/ Fundación Canaria Instituto de Investigación Sanitaria de Canarias (SESCS/FIISC)".

The people that compose the Agency's technical support team at SESCO/FIISC supporting ERN-EuroBloodNet is the following:

Role	Name
Methodologist (Coordinator)	Mar Trujillo Martin
Methodologist	Tasmania del Pino Sedeño
Methodologist	Beatriz León Salas
Methodologist	Aythami de Armas Castellano
Methodologist	Diego Infante Ventura
Methodologist	Yadira González Hernández
Information Specialist	Leticia Rodríguez Rodríguez

Table 1. SESCO/FIISC technical team supporting ERN-EuroBloodNet

CONFIGURATION OF THE EXPERT PANEL AND INVOLVEMENT OF PATIENT ADVOCATE

The action is chaired by Dr. Vincent Ribrag (Institut Gustave Roussy, France) with the support of Dr. Luca Malcovati (as ERN-EuroBloodNet leader for the CPGs and CDMTs development) and the ERN-EuroBloodNet coordination team.

As first step, a list of potential candidates was identified among ERN-EuroBloodNet experts and other colleagues not part of the network but well known among the Burkitt lymphoma field. Invitation letters were sent by the coordination team to join the action as part of the Expert Panel.

Expert Panel was configured with a total of 10 Experts from 8 Member States (Table 2). A balance among experts belonging to ERN-EuroBloodNet members and non-members was ensured (5/5). Also the inclusion of two young hematologists was considered in order to support on the systematic review process considering their higher time availability.

Finally, the group was completed with the involvement of a patient advocate to be actively involved in the development of such CPG from the beginning. An invitation letter was sent to the two ERN-EuroBloodNet ePAGs representatives involved in the Lymphoma area, from which Natacha Bolaños was chosen to be the advocate involved in the action as representative of Lymphoma Coalition. Patients representatives have a non-voting role in the Expert Panel but are expected to join the meetings, including the consensus conferences.

MS	Expert	Institution
BE	Dominique Bron	Jules Bordet Institute
DE	Dieter Hoelzer	ONKOLOGIKUM Frankfurt am Museumsufer
DK	Judit Jørgensen	Aarhus University Hospital
ES	Josep-Maria Ribera	Institut Català d'Oncologia Hospital Germans Trias i Pujol
FR	Vincent Ribrag (Chair)	Institut Gustave Roussy
FR	Clémentine Sarkozy	Institut Gustave Roussy
FR	Charles Herbaux	CHU Montpellier
IT	Pier Luigi Zinzani	Institute of Hematology "L. e A. Seràgnoli" / University of Bologna
NL	Martine E.D. Chamuleau	Amsterdam UMC
PL	Jan Walewski	Maria Skłodowska-Curie National Research Institute of Oncology

Table 2. Expert Panel for the Guideline on Burkitt Lymphoma

PICO QUESTIONS AND WORKING GROUPS

[An online meeting with the Burkitt Lymphoma whole group](#) was organized by the Chair of the action with the support of the ERN-EuroBloodNet team on January 2021 in order to introduce the Expert Panel and Patient advocate the initiative and aims (Fig 1). Key steps of the process including the direct link with SECS/FIISC in charge of the systematic review of literature and the tentative timeline was presented.

The meeting provided the perfect opportunity to share ideas on the PICO (Population, Intervention, Comparison, Outcome) questions to be answered through the CPG. An open discussion week was provided in order to refine and confirm the following final 4 PICO questions:

- 1) What are the recommendations for proper diagnosis of Burkitt Lymphoma?
- 2) What are key parameters for individual risk assessment and for guiding to therapeutic strategies?
- 3) What is the first line therapy for Burkitt Lymphoma?
- 4) What is the recommended treatment of Tumor lysis syndrome (TLS) in adults with Burkitt Lymphoma?

In addition, Expert panel was distributed according to their preferences into 4 Working Groups to be actively involved in the discussions of each question. Reference persons to be in direct contact with SECS/FIISC for the systematic review of literature were also assigned for each PICO question.

At the time of the present deliverable the systematic review of literature is ongoing with the support of the SECS/FIISC team working in close collaborations with the representatives elected for each question.

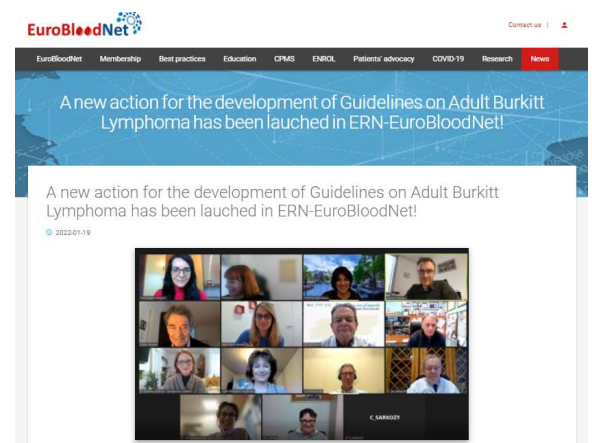


Fig 1. ERN-EuroBloodNet piece of news on the online meeting

RECOMMENDATIONS FOR DIAGNOSIS AND TREATMENT OF METHEMOGLOBINEMIA

A collaboration with the European Hematology Association (EHA) Guidelines Committee has been established aiming to promote and support the creation and adoption of guidelines for diagnosis and treatment of hematologic diseases.

The goal of the collaboration is to avoid duplication of efforts by both entities, and promoting synergies to agree one set of recommendations, to avoid discrepancies and to optimize resources in producing such guidelines. ERN-EuroBloodNet and the EHA has signed a Memorandum of Understanding (MOU) containing the terms of collaboration, including an overview of the tasks and responsibilities of each party and entering into force January 2021.

In this context, the first joint project was the development of a clinical decision making tool on Methemoglobinemia, under the co-chairing of ERN-EuroBloodNet experts [Prof. Achille Iolascon \(AOU Federico II - Naples\)](#) and [Dr. Paola Bianchi \(Foundation IRCCS Ca'Granda Ospedale Maggiore Policlinico, Milan\)](#). In the Recommendations participated multiple experts from ERN-EuroBloodNet members in different Member States.

[Recommendations for diagnosis and treatment of methemoglobinemia](#) were published at American Journal of Hematology in September 2021 with the acknowledgment of EHA and ERN-EuroBloodNet. Recommendations are also searchable and findable through the ERN-EuroBloodNet repository of CPGs and other CDMTs (Fig 2).

The screenshot displays the EuroBloodNet website interface. At the top, there is a navigation menu with options like 'EuroBloodNet', 'Membership', 'Best practices', 'Education', 'CPMS', 'ENROL', 'Patients' advocacy', 'COVID-19', 'Research', and 'News'. The main heading reads 'Search Guidelines and other CDMTs'. Below this, a search filter interface is shown with dropdown menus for 'Subnetwork' (Red blood cell defects), 'Disease group' (Red blood cell enzyme defects), 'Scope and Purpose' (S. Diagnosis and treatment), and 'Rigour of development' (B - Consensus based). A red 'SEARCH' button is visible. The search results display the title 'Recommendations for diagnosis and treatment of methemoglobinemia' along with its subnetwork and disease group details. To the right, there is a banner for the 'American Journal of Hematology' (AJH) with a red background and white text. Below the banner, the text 'CRITICAL REVIEW' and 'Open Access' is displayed, followed by Creative Commons license icons. The main title of the article is repeated: 'Recommendations for diagnosis and treatment of methemoglobinemia'. The authors listed are Achille Iolascon, Paola Bianchi, Immacolata Andolfo, Roberta Russo, Wilma Barcellini, Elisa Fermo, Gergely Toldi, Stefano Ghirardello, Davis Rees, Richard Van Wijk, Antonis Kattamis, Patrick G. Gallagher, Noemi Roy, Ali Taher, Razan Mohty, Andreas Kulozik, Lucia De Franceschi, Antonella Gambale, Mariane De Montalembert, Gian Luca Forni, Cornelis L. Hartevelde, Josef Prchal, and the text 'On behalf of SWG of red cell and iron of EHA and EuroBloodNet'.

Fig 2. Recommendations published at American Journal of Hematology available at the ERN-EuroBloodNet repository of CPGs and other CDMTs

4. CONCLUSIONS AND NEXT STEPS

The [repository of CPGs and other CDMTs on RHD](#) is publicly available on ERN-EuroBloodNet website allowing both non-experts and experts in RHD to benefit from an exhaustive database with reliable and updated clinical decision support tools, promoting the delivery of highly specialised procedures and treatments and the harmonisation of care delivery across EU.

In addition, the [search engine](#) implemented allows the findability of the CPGs and other CDMTs classified on quality domains, promoting the searchability by concrete needs of the RHD community, including: subnetwork, RHDs Disease Groups, Scope and Purpose (Prevention, Diagnosis, Treatment, and Rigour of development), or Rigour of Development (A Evidence and consensus based, B Consensus based, C Expert opinion). As next step, the classification on Quality Domains will be finalized for the Bleeding and coagulation disorders and Lymphoid malignancies.

The Top 10 priority list for CPGs and other CDMTs development identified by ERN-EuroBloodNet has allowed the targeting of the most important areas to be tackled in the frame of the network.

As the first priority identified, the CPG on Adult Burkitt Lymphoma is being created in the frame of the DG SANTE support action to ERNs for the development/upgrade of CPGs and other CDMTs. The guideline is currently in the systematic review process step and will be finalized in the next period of ERN-EuroBloodNet implementation. The second topic to be developed in the frame of DG SANTE supporting action has already been identified for the creation of a CPG for Long-term complications of haemoglobinopathies, which is expected to be initiated in the next period of ERN-EuroBloodNet implementation.

Moreover, the official collaboration with the European Hematology Association (EHA) allows the implementation of a common strategy among both bodies, leading to the publication of the Recommendations for the diagnosis and treatment on Methemoglobinemia as first target. Collaboration will continue in the next period of ERN-EuroBloodNet implementation.

Lastly, the recent conduction of the ERN-EuroBloodNet European mapping of highly specialized procedures for primary vitreoretinal lymphoma has allowed the identification of important disparities in clinical practice between physicians on diagnosis, treatment and assessment of treatment response and follow up, and therefore the high need for development of a Clinical Practice Guideline on the area that will be taken into consideration to be addressed by the ERN-EuroBloodNet in the next period of implementation. Further details can be found at Deliverable 4.5 ERN-EuroBloodNet report on the availability of highly specialized procedures for rare hematological diseases 2 (February 2022) and the peer review publication "[Primary vitreoretinal lymphoma: short review of the literature, results of a European survey and French guidelines of the LOC network for diagnosis, treatment and follow-up](#)" published in Current opinion in oncology in September 2021 with the acknowledgement of ERN-EuroBloodNet.



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