2nd ERN-EuroBloodNet Interactive Session at the EHA Congress

14th June 2019, Amsterdam

Main outcomes

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

Coordination team:

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Agenda ERN-EuroBloodNet 2nd Interactive Session at the EHA Congress

European Hematology Association Congress 2019

RAI Amsterdam at Europaplein 24, 1078 GZ Amsterdam, The Netherlands.

17:15 – 19:00

0. Call for ERNs registries: EuroBloodNet proposal and link to RADeep - María del Mar Mañú Pereira

Cross border health

1. Cross Border Health Case study - Ananda Plate, Raffaella Colombatti, Pilar Nicolás, Loris Brunetta
2. European mapping on Bone Marrow Transplant for non-oncological hematological disorders - Victoria Gutiérrez Valle, Raffaella Colombatti, María del Mar Mañú Pereira

Disease focussed initiatives

3. EuroBloodNet initiatives on Pyruvate Kinase Deficiency - María del Mar Mañú Pereira, Paola Bianchi
4. EuroBloodNet initiatives on Haemochromatosis and rare Iron metabolism disorders - Graça Porto, Dorine Swinkels, Domenico Girelli

Best practices

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7. Educational repository and Webinars programme - Patricia Aguilar-Martinez, Dominique Bron
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9. European Sickle Cell Disease network of patients associations - Ariane Weinman, Mariangela Pellegrini, Loris Brunetta

Clinical trials and research

10. EuroBloodNet sponsoring CTs - Pierre Fenaux
11. Italian Society for Thalassemia & Hemoglobinopathies" SITE: EuroBloodNet related activity report- Gian Luca Forni, Domenica Cappellini, Antonio Piga

State of the art

Call for ERNs registries

EuroBloodNet proposal and link to RADeep - María del Mar Mañú Pereira

ERN-EuroBloodNet Scientific director announced that the call "Rare disease registries for the European Reference Networks" has been launched under the 3rd Health Programme of the European Commission to support the development of rare disease registries for the ERNs. Following the call for ERNs registries on 2018 where 5 ERNs were granted to implement their dedicated registries, this call will grant the 19 remaining ERNs, accordingly in this occasion it is not a comptetitve call among ERNs. Guidance on what is expected from ERNs to be achieved has already been provided by the EC.

Cross border health

European mapping on Bone Marrow Transplant for non-oncological haematological disorders and Cross Border Health Case study – Ananda Plate, Raffaella Colombatti, Pilar Nicolás, Loris Brunetta, Victoria Gutierrez Valle and María del Mar Mañú Pereira

Two surveys were launched during last year 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: Next generation sequencing (NGS) and Bone marrow transplantation (BMT) on non-oncological disorders.

The main results from the questionnaire on BMT were presented after the analysis of 39 responses received, setting the basis **to assess potential cross border agreements between medical centres for specific diseases, e.g. BMT for adult Sickle Cell Disease patients.**

Next steps:

- Gathering of additional answers through a second wave in order to gather major evidence for analysis
- The request of a query to EBMT will be analysed in order to extract data from non-oncological disorders by center and compliment results.

As an addition action on cross border health, the agreement among an HCP from Ireland and HCP from Italy for the Bone Marrow Transplantation for Sickle Cell Disease is almost finalized.

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

Next steps:

- 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.

- CBH agreements and reimbursement process among wealth and non-wealth countries (ie. Eastern countries) is a transversal issue for all ERNs not yet solved.

Disease focussed initiatives

EuroBloodNet initiatives on Pyruvate Kinase Deficiency - María del Mar Mañú Pereira, Paola Bianchi

Diagnosis of Pyruvate Kinase deficiency (PKD) has been identified as a routine test 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

A first mapping exercise was conducted in December 2017 among ERN-EuroBloodNet members and not members including:

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.

List of participating centres available on:
https://www.eurobloodnet.eu/radeep/pkdeep/mappingoffacilities

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

Next steps:

- Conduction of a 2nd survey to better coverage of centres (estimation of prevalence) and Stratification of patients by age and severity
- Indicators for assess implementation of the recommendations
- A set of items linked to diagnosis performance for definition of EQAs implementation after the pilots
- Implementation of this methodology for other disorders as CDA and sideroblastic anaemia will be analysed.

EuroBloodNet initiatives on Haemochromatosis and rare Iron metabolism disorders - Graça Porto, Dorine Swinkels, Domenico Girelli

Several genes are involved in the signaling of hepcidin and mutations in all these genes can cause hemochromatosis. So the classification of hemochromatosis has been historically dependent on the discoveries of these iron regulatory genes. By far the most common is HFE hemochromatosis, where one single mutation in homozygosity explains more than 90% of cases and that was called type 1.

It has been raised the need of the Revision of Nomenclature to classify the Rare Hemochromatosis. This process is under discussion by the "IBIS nomenclature commission", chaired by ERN-EuroBloodNet representative Domenico Girelli. An Ibis meeting has been held was obtained on:

- Distinguish two major groups: HFE and non-HFE hemochromatosis
- Not consider as a different entity hemochromatosis due to rare mutations in HFE
- Substitute the nomenclature of "types" 1,2(a,b),3,4 by the respective mutated genes
- Separating hemochromatosis from ferroportin disease

Next steps:

Following the recently release of the EU - Platform for Rare Diseases to start the process of creating a RADeep arm on Rare Hemochromatosis.

1. Mapping the facilities available in Europe for diagnosis of the rare non-HFE hemochromatosis

   - Dissemination of a survey to identify the competent European centres and/or experts for the diagnosis of non-HFE hemochromatosis
   - Establishment of a disease specific data set in line with the EC requirements and fulfilling the RADeep objectives for non-HFE hemochromatosis

2. Revision of Nomenclature to classify the Rare Hemochromatosis (in the frame of the IBIS activities).

Best practices

Repository of guidelines and assessment of implementation - Achille Iolascon, Luca Malcovati, Amanda Bok

A list of international guidelines and recommendations gathering the most frequent guidelines used for the main RHD conditions has been produced, including a total of 116 guidelines/recommendations for the six subnetworks.

Guidelines/recommendations compiled will be classified based on quality domains in line with AGREE methodology.

Classification will be made according to:

- Level A: Evidence and consensus-based guidelines / recommendations
- Level B: Consensus-based guidelines / recommendations
- Level C: Expert opinion only includes consensus among experts

The assessment of guidelines awareness and implementation will be undertaken focusing on mandatory highly specialized procedures potentially conflictive for their extensive compliance.

Standards of Care (SoC) that should be monitored will be identified by the task force defined for the classification of the guidelines/recommendations.

Collaboration with EHA working group on guidelines will be also established for the promotion of guidelines and recommendations poorly implemented, or creation of new ones if lacking.

Telemedicine

Clinical Patients Management System - update & eLearning - Fahed Ahssini, Béatrice Gulbis

The European Commission has created the **Clinical Patients Management System (CPMS)**, a platform for sharing patients' clinical data within ERNs compliant with the new European Regulation of data protection.

Sharing of patients' data, even pseudo anonym data, is not allowed to be done by non secure vias as e-mail. The aim of this platform is to improve diagnosis and treatment in complex cases by facilitating cross border sharing of data in a secure environment.

In addition, the use of the CPMS is one of the key criteria defined by the EC for monitoring excellence of centres. Members are invited to create their profile following this link:

https://cpms.ern-net.eu/login/

ERNs are requested by the CPMS IT team at the EC to customize two areas of the platform:

- Define profiles of the experts in the panels

- Consultation form of the patient enrolled: All ERNs have one generic data set, Basic Data Set, in the CPMS.

An Extended Data Set can be developed based on the customized need of each ERN.

Implementation of customised consultation form foreseen very soon:

- Test phase for customised datasets will start subsequently.
- Feedback from experts using the platform and possible amendments to be done.

Webinars:

- Webinars will be held to clarify and help EuroBloodNet members to get used to the CPMS (Invitation to participate will be sent soon)
- These webinars will be available on the EuroBloodNet website

To participate and get your account on the CPMS please contact Fahed Ahssini (Operational Helpdesk) and you will receive a clear description of the way you should request your account and how to use the CPMS.

Email address: **fahed.ahssini@erasme.ulb.ac.be**

Continuing Medical Education

Educational repository and Webinars programme - Patricia Aguilar-Martinez, Dominique Bron

A survey has been conducted among ERN-EuroBloodNet members for the identification of **educational gaps** for both, health professionals and patients, and for the **creation of a repository on educational material.**

- A total of 21 answers from 9 countries have been compiled.
- Educational gaps identified include for ultra rare disorders:
  - Practical teaching material for professionals
  - Educational material for patients
  - Lack of European and/or national guidelines/recommendations (>very rare)

A total of 152 educational materials were compiled and classified according the criteria assigned in the template. Results and analysis are included in Deliverable 5.1 Report on educational gaps.

The possibility of expanding the survey to non-members in order to complement the results is being analysed.

Next steps:

1. Develop criteria for the classification of educational material based on Quality Domains
2. Make a repository at ERN-EuroBloodNet website
3. Identify gaps and make proposals for educational material – (for patients). For the creation of new material
4. Implementation of ERN-EuroBloodNet e-Learning platform – Project funded by CEF Telecom grant – Connecting EuroBloodNet II (Oct 2019 – Mar 2021)

Webinars for health professionals will be held 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.**

- Webinars will be conducted using the Webex Platform provided by the European Commission.
- 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).
- 1-2 webinars per month. The balance among subnetworks will be ensured, holding 2-4 webinars/year/subnetwork.

The program is foreseen to start in September 2019.

Next steps include:

1. Share the list of proposed webinars and define the final list
2. Officially invite speakers
3. Create the template for the presentation (structure…)
4. Publish in the website to block the dates and have suggestions for topics

Short stays for health professionals - Mariangela Pellegrini, Pierre Fenaux, Régis Peffault de la Tour

Paroxysmal nocturnal hemoglobinuria (PNH) and **Aplastic Anaemia (AA)** were identified during the first year of implementation as one of the areas that will benefit from organizing short stays.

- Three sites (one from France and two from Italy) with different focus (adults, pediatrics…) are foreseen to receive health professionals for training.
- Objective: 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.
- Call will be open in 2019. Candidates will be chosen by a jury according to: CV+ cover letter + CBH collaboration .

Next short fellowships will be held on **Sickle Cell Disease (SCD).**

- Four sites have been identified (France, France overseas, Italy and UK).
- Objective: To increase awareness of current management of sickle cell disease, delivering excellence in patient care education, clinical audit and stimulate research interests. Preceptorships based on clinical cases.
- Call will be open in 2020. Candidates will be chosen by a jury according to: CV+ cover letter + CBH collaboration.

European Sickle Cell Disease network of patients associations - Ariane Weinman, Mariangela Pellegrini, Loris Brunetta

ERN-EuroBloodNet is establishing a **European SCD Patients network** that will represent the umbrella of SCD National Patients Organizations in Europe. Each country will have 2 spokesmen in representation of all their national patients' organizations. Among all spokesmen a representative one will become ePAG for the ERN EuroBloodNet for SCD.

The outcomes achieved during the first Italian national Meeting in Milan, held the 29th of March 2019, were presented during the meeting.

Next steps include :

- The 29th of June, French Meeting of SCD POs
- Probabably first European Meeting the day before or after the BoN, the 14th of November

Clinical Trials

ERN-EuroBloodNet sponsoring CTs – Pierre Fenaux

Sponsor the use of **innovative drugs** in clinical trials through ERN-EuroBloodNet.

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 CDA and other rare inherited anmias (A Iolascon, O Hermine)
- Deoxygenated RBC (Hemanext)
  - SCD (P Bartolucci)
  - Refractory sideroblastic anemia (L Pascal)

Italian Society for Thalassemia & Hemoglobinopathies" SITE: EuroBloodNet related activity report - Gian Luca Forni, Domenica Cappellini, Antonio Piga

The SITE is developing a decision making algorithm for the candidate to the Thalassemia Gene Therapy. The board of this working group is made by several ERN-EuroBloodNet. In the "era of the GT", it has become imperative to establish the "setting" of patients in which this can be applied, or rather, for which it can be a real indication. The current knowledge and data of the unconventional treatment of these patients, Allogeneic Transplantation and Gene Therapy are then reported, in order to understand and then identify the best treatment available and possible for these patients, based on their characteristics.

The purpose of this "Consensus" is to identify which TDT patients can benefit and have indications for Gene Therapy.

The idea is to create a dynamic and updatable tool; structured to allow two levels of consultation:

1. A Flow chart in which the conclusive practical indications relating to the various chapters and the various questions are reported.

2. The various chapters that deal the topic in detail.

Next steps:

- Interaction with the "National Hemoglobinopathies Network" to acquire information on the number of specialized treatment centers and of the patients suffering from these diseases.
- Recognition of existing information flows.
- Definition of the data set to be entered in the Register.

3rd Board of the Network Meeting will be held next 13th and 14th November 2019 in Barcelona including parallel sessions on dedicated related projects. If you are willing to attend send an email to Victoria.gutierrez@vhir.org