EuroBloodNet
European Reference Network in Rare Hematological Diseases

# Criteria defined by the Network for Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis

The following information defines the specific criteria for our proposal for a European Reference Network (ERN) for Rare Hematological Diseases, EuroBloodNet. Each health care provider willing to be member of our ERN has to fulfil these criteria. These evidence based criteria intend to be realistic while ensuring a high level patient care.

The following information corresponds to the following points in the HCP application form:

**1) Point 7_Table in Page 6** Diseases, conditions and highly specialized interventions: it includes not only diseases but also highly specialized interventions, treatments eg bone marrow transplantation

**2) Point 11_Table in Page 9** 10 of the 16 "Diseases, conditions and highly specialized interventions" defined in point 7 needs to be quantified

**3) Point 12_Table in page 11 "Multidisciplinary team"**Up to 16 Health care professionals have to be defined: position, training and number of patients/procedures by year (for assure expertise)

**4) Point 13_Table in page 12 "Specialised equipment, infrastructure and IT"** Up to 16 Specialised equipment, infrastructure and IT used by the HCP to support diagnosis, care and treatment

**5) Point 21_Table in page 18 "Clinical outcome data"** Up to 22 relevant clinical outcomes related to the Rare or complex disease, condition or highly specialized interventions defined

- Subthematic area of expertise:
    - Rare red blood cell defects
    - Bone marrow (BM) failure and rare haematopoietic disorders
    - X **Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis**
    - Rare bleeding-coagulation disorders
    - Myeloid malignancies
    - Lymphoid malignancies

**1) Point 7_Table in Page 6** Diseases, conditions and highly specialized interventions: it includes not only diseases but also highly specialized interventions, treatments eg bone marrow transplantation

| Subthematic area of expertise | Rare or complex disease, condition or highly specialized interventions | ICD / Orphanet Code |
|---|---|---|
| Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis | non-HFE related hereditary hemochromatosis: (HH types 2A, 2B, 3 and 4A,4B ), TFH1-Related Hemochromatosis (type V), Hereditary Hyperferritinemia Cataract Syndrome (HHCS) | Orphanet (OMIM) nºs: 79230 (602390 and 613313); 225123 (604250); 139491 (606069); FTH1: 247790 (615517); FTL: 163 (600886) |
| Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis | HFE-related hereditary hemochromatosis with established severe clinical expression or due to very rare mutations in HFE | Orphanet (OMIM) nºs:139489 (235200) |
| Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis | Low iron availability for erythropoiesis: Iron Refractory Iron deficiency Anemia (IRIDA), Aceruloplasminemia (ACP)_ | Orphanet (OMIM) nºs: TMPRSS6: 209981 (206200); ACP: 48818 (604290) |
| Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis | Rare defects in iron acquisition and transport: Atransferrinemia, Microcytic anemia with iron loading (DMT1), Sideroblastic anemia (STEAP3) | OMIM nºs: TF: 209300; DMT1: 206100; STEAP3: 615234 |
| Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis | Defects in heme synthesis or Fe-S cluster biogenesis: Sideroblastic anemias (SLC25A38, GLRX5; HSPA9), XLSA with ataxia (ABCB7), XLSA (ALAS2) | OMIM nºs: SLC25A38: 205950; GLRX5: 205950; HSPA9: 182170; ABCB7: 301310; ALAS-2: 300751 |
| Hemochromatosis and other rare genetic disorders of iron metabolism and heme | Complex molecular diagnosis, predictive testing with genetic counselling and prenatal | |

| | | |
|---|---|---|
| synthesis | diagnosis | |
| Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis | Iron overload management: iron chelation prescription and monitoring | |
| Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis | Biochemical and hematology tests, validated and accredited for clinical use, including Serum Hepcidin-25 (for IRIDA), ferritin, transferrin, iron, sTfR, Hb, MCV. | |
| Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis | Bone marrow smears for ring sideroblasts | |
| Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis | MRI-T2 for iron monitoring | |
| Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis | Phlebotomy unit and erythrocytapheresis, if needed | |
| Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis | Blood transfusion management, care of immunized patients | |
| Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis | Bone marrow transplant for some disorders and rejection management | |
| Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis | Liver unit facilities (biopsy, access to liver transplant center), cardiovigilance, joint replacement | |

**2) Point 11_Table in Page 9** 10 of the 16 "Diseases, conditions and highly specialized interventions" defined in point 7 needs to be quantified

| Specific diseases, conditions and highly specialized interventions | Measure | Evidence |
|---|---|---|
| non-HFE related hereditary hemochromatosis: (HH types 2A, 2B, 3 and 4B) and ferroportin disease (HH type 4A), TFH1-Related Hemochromatosis (type V), Hereditary Hyperferritinemia Cataract Syndrome (HHCS) | Number of patients with non-HFE related HH or ferroportin disease (active) per year | 5 |
| HFE-related hereditary hemochromatosis with established severe clinical expression or due to very rare mutations in HFE | Number of patients with established severe HFE related HH (active) per year | 10 |
| Low iron availability for erythropoiesis: Iron Refractory Iron deficiency Anemia (IRIDA), Aceruloplasminemia | Number of patients per year | 5 |
| Rare defects in iron acquisition and transport: Atransferrinemia, Microcytytic anemia with iron loading (DMT1), Sideroblastic anemia (STEAP3) | Number of patients per 5 years | 1 |
| Defects in heme synthesis or Fe-S cluster biogenesis: Sideroblastic anemias (SLC25A38, GLRX5; HSPA9), XLSA with ataxia (ABCB7), XLSA (ALAS2) | Number of patients per year | 2 |
| Bone marrow transplant unit | Number of procedures per year (overall) | 10 |
| Liver disease unit | Number of procedures (liver biopsy) per year | 5 |
| MR Imaging | Number of procedures per year (overall) | 10 |

**3) Point 12_Table in page 11 "Multidisciplinary team"** Up to 16 Health care professionals have to be defined: position, training and number of patients/procedures by year (for assure expertise)

| Healthcare professional | Training and qualifications | Nº procedures/patients per year |
|---|---|---|
| Hematologist, Internist, pediatrician or hepatologist: as primary treating physician for hemochromatosis | Expertise > 3 years | 10 |
| Hepatologist, rheumatologist (or orthopedics specialist), cardiologist and endocrinologist: as secondary treating physicians for hemochromatosis | Expertise > 3 years | 2 |
| Nurse | Expertise in haemochromatosis > 3 years | 10 |
| Hematologist OR pediatrician-hematologist: as primary physician for anemias due to genetic disorders of iron metabolism and heme synthesis | Expertise > 3 years | 5 |
| Internist as secondary physician for anemias due to genetic disorders of iron metabolism and heme synthesis | Expertise > 3 years | 2 |
| Laboratory specialist | Expertise > 3 years | 30 |
| Geneticists | Expertise> 3 years | |
| Radiologist | Expertise in iron overload assessment > 3 years | 10 |
| Clinical Geneticist/Genetic counselor | Expertise > 3 years | 20 |
| Pathologists | Expertise in interpretation of liver biopsies in patients suspected for iron overload | 3 |

**4) Point 13_Table in page 12 "Specialised equipment, infrastructure and IT"** Up to 16 Specialised equipment, infrastructure and IT used by the HCP to support diagnosis, care and treatment

| Specific diseases, conditions and highly specialized interventions | Specific equipment, infrastructure and information technology (IT) |
|---|---|
| Complex molecular diagnosis, predictive testing with genetic | Accredited Molecular Genetics, Hematology and clinical chemistry Laboratories |

| | |
|---|---|
| counselling and prenatal diagnosis | |
| Phlebotomy unit and erythrocytapheresis, if needed | Facility for phlebotomy and erythrocytapheresis. |
| MRI-T2 for iron monitoring | Well equipped Radiology Department, withMRI-T2* for iron monitoring. |
| Bone marrow transplant for some disorders and rejection management | Facilities and expertise in Hematopoietic stem cell transplantation (for severe forms of Sideroblastic anemia). |

**5) Point 21_Table in page 18 "Clinical outcome data"** Up to 22 relevant clinical outcomes related to the Rare or complex disease, condition or highly specialized interventions defined

| Rare or complex disease, condition or highly specialized interventions | Clinical outcome | Evidence (quantifier) |
|---|---|---|
| Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis | % Hereditary hemochromatosis patients with ferritin < 50 µg/L | < 20% |
| Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis | % Hereditary hemochromatosis patients with ferritin > 300 µg/L, 6 months after the diagnosis | < 5 % |
| Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis | % Iron loading anemia patients with ferritin > 350 µg/L | < 10% |
| Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis | % of patients with inherited defects in iron metabolism, initially diagnosed with MDS | < 5% |
| Rare anemia (IRIDA) | Hb < 5.0 mmol/L<br>Ferritin> 550 µg/L | < 3% of patients<br>< 3 % of the patients |
| Hemochromatosis | Development of hepatocellular carcinoma (HCC)during life | < 5 % of the patients |
| Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis | % of patients diagnosed within 3 months after referral to EC | >90% |
| Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis | % mortality of patient with iron overload disease and HCC | < 50% |