ENROL STUDY PROTOCOL

European Rare Blood Disorders Platform (ENROL)

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DOCUMENT INFORMATION

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PROTOCOL SYNOPSIS

Study Title:

European Rare Blood Disorders Platform (ENROL)

Study Objectives:

The European Rare Blood Disorders Platform (ENROL) is conceived in the core of the European Reference Network on Rare Hematological Diseases (ERN-EuroBloodNet), as the umbrella platform for both new and already existing registries on Rare Hematological Diseases (RHDs) avoiding fragmentation of data by promoting the interoperability standards for patient registries.

ENROL aims at mapping demographics, diagnosis methods, genetic data, main clinical manifestations and treatments at the EU level by enabling the connection, upgrading and building of EU patients registries in line with EU data protection and interoperability standards with the following major objectives:

1. **Promoting research**: allowing the identification of patient cohorts to facilitate the development of collaborative projects on basic and clinical research on RHD
2. **Epidemiological surveillance**: pooling of available data on registries and databases across European countries to monitor trends and provide essential epidemiologic information on RHD while enabling the generation of evidence for the optimum allocation of resources and health planning

For this, ENROL will obtain comparable EU data for RHD on demographics, survival rates, diagnosis methods, genetic information, main clinical manifestations and treatments by promoting the interoperability standards for patient registries in line with the European Platform on Rare Disease Registration (EU RD Platform). ENROL is officially endorsed by the European Hematology Association (EHA).

Methodology:

Data on patients with RHDs will be collected retrospectively and prospectively at the time of inclusion on the registry and at 12-month intervals for all registered patients.

The ENROL strategy for data gathering combines the exhaustiveness of data collection at EU level for health planning and epidemiological purposes, with a higher level of RHD data granularity for promoting research and identification of patients' cohorts.

Accordingly, the platform has been designed to integrate data from any available sources, including Healthcare providers (ERN-EuroBloodNet members / Other EU healthcare providers) and EU/national/local existing registries. Data entry is also allowed with different levels of granularity to pursue ENROL aims, including counts/aggregated level data to increase data exhaustiveness at the EU level required for the epidemiological surveillance, and pseudonymised individual level data to promote research and facilitate the identification of trial groups.

As defined in GDPR Art. 26, a Joint Controllership is being established where the institutions conforming the Consortium (VHIR/HUVH, ERASME, CING and AP-HP) for the jointly determine the purposes and means of processing and assume equal responsibilities in terms of data protection.

Data processing and analyses will be conducted in various sub studies, after every 1000 patients included in the European Registry and/or at the end of each interim follow-up period (every 12 months).

Disease coverage

The study population consist of both males and females aged from 0 to 100 year old diagnosed as RHD according to ORPHANET classification (ORPHA 97992), including myeloid and lymphoid tumors (ORPHA 68347), rare anaemia disorders (ORPHA 108997), rare coagulation disorders (ORPHA 98429), and polycythemia (ORPHA 98427), and further complemented with rare hereditary hemochromatosis (ORPHA220489), included in the disease scope of ERN-EuroBloodNet following a request from well-established patient groups and experts.

Accordingly, ENROL disease coverage results in more than 450 different entities with differential clinical and etiological features i.e. oncological vs non-oncological, hereditary vs acquired, or significant difference frequency, among others, which can be classified into the following disease groups:

- RAD: Inherited Rare Anaemia Disorders, including inherited Bone Marrow Failures
- BMF: Acquired Bone Marrow Failures

- Bleeding: Rare bleeding-coagulation disorders and related diseases
- HH-Iron: Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis
- Myeloid: Myeloid malignancies
- Lymphoid: Lymphoid malignancies

ENROL dataset has been conceived in a bottom-up design for ensuring the capture of the common elements for rare diseases in line with the EU recommendations and with the EU RD platform, and the key features common for the whole spectrum for RHDs. Furthermore, the latest level can be stepped up for the definition of domain specific elements that support the in-depth analysis.

In the spirit of ENROL aims to promote the connection and linkage of available data sources and the creation of new registries where lacking. ENROL promotes collaborations for supporting the a) upgrade the existing registries and b) create new European registries in compliance with the standards of interoperability and ENROL policy. Collaboration agreements will be in place for the transfer of a subset of the data elements gathered to ENROL.

Study Duration and funding

An extensive recruitment period and follow-up, as well as geographical coverage, is desirable for long-term sustainability of the European Epidemiological Platform. Accordingly, ENROL has not an expected ending date but continue the pooling and processing of data for an indeterminate period of time.

ENROL is co-funded by the Health Programme of the European Union under the call for proposals HP-PJ-2019 on Rare disease registries for the European Reference Networks. GA number 947670.

1. BACKGROUND

1.1 RARE HAEMATOLOGICAL DISEASES: COMMON FEATURES AND NEEDS

The European Reference Network on Rare Hematological Diseases (ERN-EuroBloodNet) was established by the European Commission in 2017 aiming at improving the healthcare and overall quality of life of patients with a rare haematological disorder (RHD) by facilitating best practice sharing for safe and high-quality cross-border healthcare while developing evidence-based clinical tools and cost-effective treatments. ERN-EuroBloodNet counts with 96 Members healthcare providers from 18 EU Member States nationally recognized as highly specialized centers in the management of RHD patients.

ERN-EuroBloodNet disease coverage results in more than 450 different RHDs entities with differential clinical and aetiological features i.e. oncological vs non-oncological, hereditary vs acquired, or significant difference frequency. RHDs can cause chronic health problems and many of them are life-threatening requiring numerous resources and multidisciplinary teams for their correct diagnosis, management, and treatment, representing a public health challenge.

With the possible exception of classical myeloma and chronic lymphocytic leukaemia, haematological diseases are rare (ORPHA97992), including myeloid and lymphoid tumours (ORPHA 68347), rare anaemia disorders (ORPHA 108997), rare coagulation disorders (ORPHA 98429), and polycythaemia (ORPHA 98427). Rare hereditary haemochromatosis (ORPHA220489) was also included in the disease scope of ERN-EuroBloodNet following a request from well-established patient groups and experts. Thus, ERN-EuroBloodNet disease coverage results in more than 450 different entities with differential clinical and etiological features i.e. oncological vs non-oncological, hereditary vs acquired, or significant difference frequency, among others.

Most of RHDs can cause chronic health problems and many of them are life-threatening requiring numerous resources and multidisciplinary teams for their correct diagnosis, management, and treatment, representing a public health challenge.

Many oncological RHD are chronic, requiring repeated cycles and associated with long-term sequelae. Survival and prevalence are important indicators of outcomes and the resources required for planning public health provision. Most studies on oncological RHDs are not general hospital-based and reflect more often selected patients. Their results, therefore, may not reflect the general situation of the entire population. In this context, Public Health planning requires population-based information, such as that provided by cancer registries. Nevertheless, the classifications of oncological RHD used in cancer registries could be improved since they are not always up-to-date or compatible with clinical classifications i.e. insufficient use of molecular information (cell surface markers, cytogenetics, tumour gene mutations).

Haemophilia A and B are the most frequent inherited bleeding disorders. Together with von Willebrand disease, a defect of primary haemostasis associated with a secondary defect in coagulation factor VIII (FVIII), these X-linked disorders include 95% to 97% of all the inherited deficiencies of coagulation factors. The other 3-5% is represented by less common inherited disorders i.e. fibrinogen, prothrombin, factors V, combined V+VIII, VII, X, XI and XIII. These disorders are inherited in an autosomal recessive manner and their prevalence is approximately 1:500,000. Their ultra-rare prevalence prevents the development of therapeutic options for these patients.

Rare Anaemia disorders (RADs) are often chronic conditions that evolve towards multi-organ damage requiring the involvement of multiple medical and paramedical specialists. If RADs are characterized by anaemia, in haemolytic RADs, the balance between haemolysis (early destruction of red blood cells) and erythropoiesis will determinate the level of anaemia and clinical severity of the disease. Meanwhile, in hypo or non-regenerative RADs a failure or malfunctioning of the bone marrow is present. Common symptomatic treatments include regular red blood cell transfusions and splenectomy. Today, the only curative treatment is the hematopoietic stem cells transplantation; gene therapy is still limited to clinical trials. Research on druggable targets correcting the balance between haemolysis and erythropoiesis will provide benefit to every severe RAs forms. Accordingly, research on new treatment options and / or development of clinical trials could be planned to cover several RADs groups, thus increasing the target group and the robustness of evidence.

1.2 EUROPEAN CONTEXT OF RARE HAEMATOLOGICAL DISEASES EPIDEMIOLOGICAL SURVEILLANCE

Despite the high number of RHD entities, as for other rare diseases (RDs), it is often challenging to bring together sufficient patient data, due to their low prevalence compounded by the fact that problems often arise in achieving an accurate diagnosis, especially for less prevalent diseases. Moreover, standards governing collection, organization, or availability of RD patient data have been lacking until recently, leading to large number of unstructured and non-interoperable sources of information at national, regional, and local levels that have been running for last decades.

This fragmentation of data has a direct impact on RHDs target groups and stakeholders. Patients who often feel isolated and, on many occasions, have no options for curative treatments, researchers and clinicians who are unable to reach critical numbers for

engaging basic and clinical research supporting development of new treatment options, and health authorities who lack epidemiological and disease burden data for the allocation of resources for best health planning. In addition, underrepresentation of ultra-rare RHDs in coding systems hampers tracing RHD patient pathways and estimating the global number of persons living with RHDs and their access to precise diagnosis and new option for treatments.

Aiming to cope with this fragmentation of data, the Directive 2011/24/EU on the application of patient rights in cross border healthcare seeks to facilitate access to healthcare for EU citizens and encourage cooperation between EU Member States (MS) in the field of health. In this directive, there is a crucial article regarding the implementation of registries. Accordingly, several MS have developed national strategies to keep track of RD patients in the country, including codification and registering of RD patients. In addition, national scientific societies support several disease specific registries as showed in May 2019 Orphanet Report Series report 'Rare Disease Registries in Europe', there are 753 disease registries in Europe. In the RHD context, a total of 242 total of registries with a European Member State (EU-MS) coverage, including also non-European countries coordinating initiatives with a global and international coverage were found through an exploratory exercise conducted. However, despite all those initiatives, fragmentation, and lack of interoperability between the data sources still is to date a key obstacle for the sharing and pooling of data required to sustain epidemiological, clinical, translational, and pharmacological research.

1.3 EUROPEAN COMMISSION STRATEGY FOR CONNECTING RARE DISEASE PATIENT REGISTRIES

The Council of the European Union recommended that, in the field of rare diseases, MS consider supporting at all appropriate levels, including the EU level, for epidemiological purposes, registries and databases, whilst being aware of independent governance. In order to support this process and, in particular, the interoperability of data in RD registries, the Directorate F (Health, Consumers and Reference Materials), the Health in Society Unit (F.1) developed in collaboration with DG SANTE, the European Union Rare Disease Platform (EU RD Platform).

The EU RD Platform copes with the fragmentation of RD patient data contained in hundreds of registries across Europe. This is ensured by the European RD Registry Infrastructure (ERDRI), composed of (1) the European Directory of Registries (ERDRI.dor), a key element in the provision of a web hub for RD registries, (2) the Central Metadata Repository (ERDRI.mdr) and (3) the pseudonymization services. Altogether they make for the first time RD registries' data searchable and findable at EU level.

Furthermore, the European Commission, under the 3rd Health Programme launched the the call HP-PJ-2019 for supporting the development of RDs registries for the ERNs aiming to enable building, upgrading, linking and making interoperable registries covering the diseases of each ERN. The European Rare Blood Disorders Platform (ENROL) was granted (GA 947670) as the ERN-EuroBloodNet umbrella for existing and new registries on RHDs, aiming at avoiding fragmentation of data by promoting the standards for patient registries' interoperability in line with the EU RD Platform.

2.ENROL

The European Rare Blood Disorders Platform (ENROL) is conceived in the core of the European Reference Network on Rare Hematological Diseases (ERN-EuroBloodNet), as the umbrella platform for both new and already existing registries on Rare Hematological Diseases (RHDs) avoiding fragmentation of data by promoting the interoperability standards for patient registries in line with the EU RD Platform. ENROL is officially endorsed by the European Hematology Association (EHA).

ENROL's Principle is to maximize public benefit from data on RHDs opened-up through the platform with the only restriction needed to guarantee patient rights and confidentiality, in agreement with EU regulations for cross-border sharing of personal data. Accordingly, ENROL aims at EU-wide mapping of demographics, survival rates, diagnosis methods, genetic information, main clinical manifestations and treatments in order to obtain epidemiological figures and identify trial cohorts for basic and clinical research.

To this aim, ENROL aims to promote the connection and linkage of available data sources and the creation of new registries where lacking, promoting collaborations for the **a) upgrade the existing registries and b) create new European registries in compliance with the standards of interoperability and ENROL policy.** Collaboration agreements will be in place for the transfer of the data elements gathered to ENROL (see also Section 4. Investigational plan)

2.1 GOVERNANCE

The overall governance of ENROL is undertaken by a Consortium formed by the Institutions of the Principal Investigators (PIs) of the platform:

- Vall d'hebron Research Institute - Vall d'Hebron Research Institute - University Hospital Vall d'Hebrón (VHIR/HUVH), Barcelona, Spain. PI: Dr Maria del Mar Mañú Pereira
- Hôpital ERASME (ERASME), Brussels, Belgium. PI: Prof Béatrice Gulbis
- Cyprus Institute of Neurology and Genetics (CING), Nicosia, Cyprus. PI: Dr Marina Kleanthous
- Assistance Publique - Hopitaux de Paris (AP-HP), France - PI: Prof Pierre Fenaux

This consortium is ENROL's decision-making body regarding the following functions:

- To define ENROL's global strategy
- To define ENROL's Policy ensuring General Data Protection Regulation (GDPR) compliance
- To negotiate financial agreements with sponsors
- To develop the IT solution with adequate safeguards for secure data exchanging

VHIR/HUVH is responsible for the scientific protocol of the platform, ERASME is responsible for the medical writing, CING is responsible for the development of the IT platform and processing of data according to the Study protocol, and AP-HP is responsible for the actions concerning empower patients' community on their decision taken regarding participation on registries. As defined in GDPR Art. 26, a Joint Controllership is being established where the institutions conforming the Consortium (VHIR/HUVH, ERASME, CING and AP-HP) for the jointly determine the purposes and means of processing and assume equal responsibilities in terms of data protection. Respective roles, rights and relations among parties forming the Consortium as well as responsibilities for compliance with the obligations under GDPR are defined in the Consortium Agreement.

Steering Committee (SC) is composed by the Consortium PIs, Domain disease experts contributing to ENROL, ERN-EuroBloodNet European Patients Advocacy Groups (ePAGs) and patient representatives, IT specialist and Platform manager. The SC is in charge of defining research protocol including research questions and definition of common data elements and their update on time as required, as well as drafting the Policy for data access and publishing.

Data Access Committee (DAC) is composed by the SC, and legal and ethical experts. The DAC is in charge of approving and implementing the Policy for data access and publications, ensuring the good use of data assets. The DAC has therefore a key role for reviewing and approving requests for data access received, as well as the anonymised figures published.

2.2 LEGAL FRAME

In agreement with ENROL's principles, a legal frame for secure sharing and re-use of data on patients affected by RHD has been established for enabling both entering certified medical data from available sources and re-use of data by third parties.

The following diagram summarizes the pathways for ENROL data entry, data processing and data request:

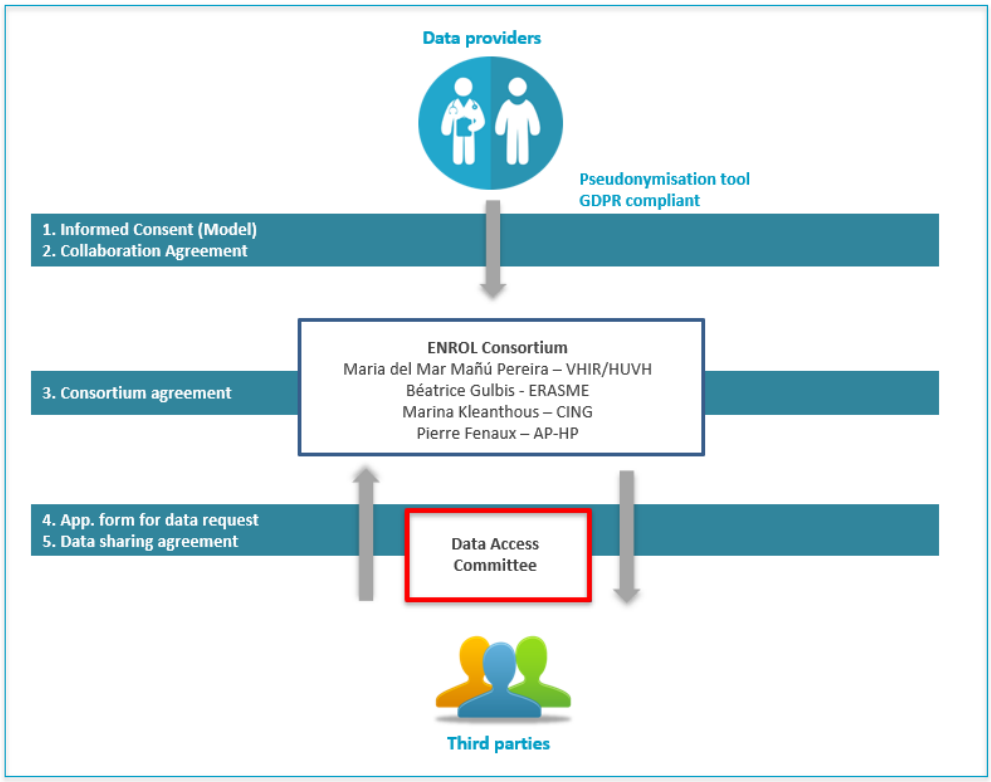

Fig 1 . ENROL data flow

Data providers

Any legal entity providing data to ENROL, including:

- Healthcare providers (ERN-EuroBloodNet members / Other EU healthcare providers)
- European/national/regional registries

Third parties

Any stakeholder (legal entity) in any country (including non-EU member states) with interest on RHDs, including:

- Healthcare providers (ERN-EuroBloodNet member or non member)
- Researchers from both public and private institutions
- Patients associations
- Health authorities
- Regulatory bodies (Health technology assessment, EMA…)
- Industry

Legal and ethical documents:

1- Informed consent
2- Collaboration agreement (from Provider of data to ENROL)
3- Consortium Agreement
4- Application form for data request
5- Data sharing agreement (from ENROL to User of data)

Legal and ethical documents for provision and request of data will be publicly available at ENROL website.

ENROL Policy enables participating stakeholders to comply with all legal and ethical considerations that apply to the processing and use of sensitive, personal information and health data.

3. STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVE

To collect and to describe demographics and epidemiological data of any type of RHDs according to ORPHA classification, which includes, among others, the following disease groups: Inherited Rare Anaemia Disorders including inherited Bone Marrow Failures, Acquired Bone Marrow Failures, Rare bleeding-coagulation disorders and related diseases, Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis, Myeloid malignancies, Lymphoid malignancies, in order to assess the incidence and prevalence of RHDs patients in Europe.

In the spirit of ENROL's aim to promote the connection and linkage of available data sources and the creation of new registries where lacking, ENROL promotes collaborations for supporting the a) upgrade the existing registries and b) create new European registries in compliance with the standards of interoperability and ENROL policy.

3.2 SECONDARY OBJECTIVES

1. To collect and to describe clinical manifestations and treatments of RHDs patients in order to:
    a. Estimate the population frequency of each RHD disease group and disease survival
    b. Estimate the diagnosis delay
    c. Estimate the attractiveness of Rare Disease centres in the health professional's community and the care pathway
    d. Appreciate method used for diagnosis
    e. Identify samples for research/clinical trials
    f. Estimate disease severity: Stratification of patients based Clinical manifestations and Treatments
    g. Assess the use of specific treatments and the possibility to include patients for research/clinical trials: Main treatments
    h. Provide a general information on research activities: Patients involved in a protocol
2. Investigate the relationship between:
    a. Clinical characteristics at inclusion and during follow-up
    b. Treatments received
    c. Responses to treatment as defined in the treatment section
3. Engaging research: allowing the identification of patient cohorts to facilitate the development of collaborative projects on basic and clinical research on RHD
4. Reduction of health inequalities: enabling the generation of evidence for the optimum allocation of resources and definition of health policies that lead to reduced inequalities across Member States with respect to access to care
5. Surveillance: pooling of available data on registries and databases across European countries to monitor trends and provide essential epidemiologic information on RHD

4. INVESTIGATIONAL PLAN

4.1 Overall Study Design

ENROL strategy has been defined for comprehensive RHD data gathering at the EU level comprising the combination of different types of sources of data and level of granularity for data transfer. Accordingly, ENROL's strategy for data gathering addresses ENROL's two objectives through the combination of the exhaustiveness of data coverage at EU level, for health planning and epidemiological purposes, with the RHD granularity, for promoting research. Therefore, the design of ENROL platform allows the integration from data from any EU source and offers the possibility of available types of sources' contribution through different levels of data granularity:

Considering the different **types of sources of data**, one of the pillars for ENROL strategy for data gathering is to build a platform that will be open to any EU data provider willing to contribute to ENROL, including:

- Healthcare providers (ERN-EuroBloodNet members / Other EU healthcare providers)
- European/national/regional registries

Moreover, taking into consideration the challenges of the fragmentation of existing data at both legal and especially technical aspects, ENROL strategy for data gathering also envisages the gathering of the different **types of data granularity level** as defined:

- Count: a total number of patients in the registry according to a condition or characteristic
- Aggregated: number of patients with a condition or characteristic defined including a basic statistic (ie. the mean and the standard deviation of the hemoglobin level)
- Pseudonymised patient level: patients' individual data transferred to the platform with the pseudonym generated at the local level prior the transfer. Correlation among patient identity and data is maintained always at the local site.

ENROL data elements (Annex I) has been designed with the following 3 levels of depth for the capture of transversal and disease specific elements according to the different concrete needs. As the registry evolves, data elements will be reviewed by the Steering Committee for assessing if an update shall be required.

1. Rare Diseases Common Data Set (RD-CDS) - set of mandatory parameters common to all RDs, essential for ensuring interoperability among European structures for RDs.

One of the first important building block for the EU RD platform is the 16 RD core data elements released by the EU-RD-Platform The document describes the 16 data elements considered to be essential to enable further research, referring to: patient's personal data, diagnosis, disease history and care pathway, as well as information to be provided for research purposes.

All existing and new RD registries across Europe are recommended to use this standard as the basis for their data collection activities. ENROL has included the data elements defined as part of the mandatory elements of the data set.

2. Rare Haematological Diseases Common Data Set (RHD-CDS) - set of mandatory parameters common to all RHDs aiming to answer ENROL objectives

Set of parameters common to all RHDs and of high interest for epidemiological surveillance and generation of patients cohorts, patient stratification according to severity and treatment options.

3. Domain specific RHD-CDS (RHD-DDS) - set of mandatory/optional parameters common to concrete domains

ENROL modular structure allows the expansion of the RHD-CDS with specific modules of mandatory and/or optional parameters for the registration of patients capturing the specificities on very concrete areas while enhancing specific research projects, i.e. disease-specific diagnosis methods, research oriented modules for development of artificial intelligence.

For each parameter included in the ENROL dataset, the data types, formats, and interactions with other parameters leading to the final ENROL dataset are defined.

International codification schemes have been implemented in ENROL dataset for disease definition (ORPHA, ICD/10/11), observed phenotypes (HPO), laboratory parameters (LOINC) and biomedical concepts (NCI). The use of these standards is cornerstone to achieve the FAIRification of data while promoting interoperability and connection with other platforms and data sources.

In addition, according to the periodicity they are captured, elements can be gathered: a) Longitudinal: Updated every 6 months - all the values are kept in the platform (previous and current introduced), b) Updated: Updated annually - Previous values are not kept (removed from the platform) only the latest value introduced is kept (e.g., a surgery performed), c) Fixed: Not possible to edit, only entered once.

In this study, no clinical, instrumental, laboratory assessments, or therapeutic intervention will be performed other than those required for disease management according to local best practice.

4.2 Study Population

The ENROL registry will be limited to patients diagnosed as RHDs according to ORPHANET classification (ORPHA 97992), which includes among others the myeloid and lymphoid tumors (ORPHA 68347), rare anaemia disorders (ORPHA 108997), rare coagulation disorders (ORPHA 98429), and polycythemia (ORPHA 98427), and further complemented with rare hereditary hemochromatosis (ORPHA 220489).

Inclusion Criteria

Patients must meet all of the following criteria to be included in the ENROL Registry:

- Age from 0-100, both female and male
- Diagnosed as RHDs according to ORPHANET classification
- Able and willing to provide the written informed consent (patient or legal representative for minors) if needed according to national legislations.

Exclusion Criteria

- Patients diagnosed as traits, or trait condition for other recessive RHDs

Follow-up & withdrawal from the Study

Patients will be followed until termination of follow-up (i.e. death, withdrawal, loss to follow-up, or termination of follow-up period). Patients will be withdrawn from the study in case of:

- Withdrawal of consent. A patient may withdraw consent at any time, without providing a reason.

5. ORGANIZATION AND RESPONSIBILITIES

5.1 OVERALL ORGANIZATION

The registry is built as a central international platform for registration of data collected by centres (referral sites) sometimes in the context of their local/national registries.

5.2 STEERING COMMITTEE

The Steering Committee (SC) is responsible for the general design (i.e. study protocol, common data elements), conduct, and overall progress of the Registry, including its revision over time by updating when required (ie. Revision of common data elements). Proposed research questions (sub studies) as well as statistical analysis plans have to be approved by the SC. Finally, it is in charge of drafting the Policy for data access and publishing.

SC is composed by the Consortium PIs, Domain disease experts contributing to ENROL, ERN-EuroBloodNet European Patients Advocacy Groups (ePAGs) and patient representatives, IT specialist and Platform manager.

During the inclusion period, the SC will meet at least once per year in a plenary session or/and by teleconference if necessary. The project manager will be responsible for drafting the minutes of each meeting and circulating this document after approval.

5.3 DATA ACCESS COMMITTEE

Data Access Committee (DAC) has the overall aim to promote the re-use of the data collected in ENROL while ensuring protection of data subjects, and specifically is in charge of approving and implementing the Policy for data access and publishing, ensuring the good use of data assets.

DAC is formed by SC and Legal and ethics experts.

5.4 PROJECT MANAGEMENT

Project management (PM) is responsible for the general day-to-day coordination and execution of general tasks of the Registry (i.e. administrative, financial, contractual, newsletters). It is also responsible for the day-to-day management of the Registry, and to advice / prepare proposals for the SC. The PM consist of Consortium PIs and project managers in the related sites.

The PM is responsible for the overall coordination of the project in the participating countries. This includes the arrangement of support for the contract duties, the distribution of sites metrics, such as the number of patients included, coordination of the referral sites and the organization of Site Training. The PM organizes all meetings, prepares and distributes the agenda and minutes. Finally, the PM supports the preparation of publications. The PM is responsible for the design and maintenance of the different sections of ENROL website.

The PM will meet every 12 months in a plenary session (during and after completion of recruitment) and TC will be scheduled on demand. The PM is responsible for the preparation of the minutes of each meeting and circulation of this document. It is the duty of the project manager to report the important issues to the members of the SC.

5.5 PLATFORM DEVELOPMENT AND STATISTIC UNIT

The Platform development and Statistics Unit is responsible for the design and maintenance of the core database, data transfer algorithms. The unit prepares working instructions related to the data entry and cleaning, executes the data cleaning and provides a database lock while prepares and executes the statistical analysis. It provides statistical support during the preparation of publications and provides metrics by site.

6. STATISTICS

The Platform development and Statistics Unit is responsible for the development of the details of the statistical analysis plan. The detailed statistical analysis plan has to be approved by the SC. This also applies whenever changes in the analysis plan are being considered.

6.1 SAMPLE SIZE

This study is exploratory in nature. Thus, the estimated sample size is not based on a statistical hypothesis, but on an estimation of the number of patients who are diagnosed with RHD per centre in an observation period and sufficiently large to perform some subgroup analyses.

6.2 COLLECTION OF CLINICAL VARIABLES

All data collected for each patient are displayed in the patient data listings. Unless otherwise stated, *baseline* is defined as the first observation at the time of diagnosis. Each value is classified as falling above, below or within normal limit. It is impossible to use a single central laboratory for all parameters and all patients. However, to avoid the issue of collecting hundreds of normal ranges, standard normal ranges will be defined and applied for the purpose of statistical analysis.

6.3 DEMOGRAPHICS AND DISEASE MANAGEMENT

Descriptive analyses will be undertaken at the end of the follow-up period using standard statistical methods to examine the subjects' demographics, disease characteristics and management of these disorders. Interim analyses are described in 6.5.

Time-to-event analyses, namely Kaplan-Meier and Cox proportional hazard regression will be used to estimate overall survival:

- The proportion (with 95% CI) of patients that has died during follow-up. The median, range and 95% CI for survival will be calculated. Overall survival is calculated for all patients from the date of RHDs diagnosis to the date of death from any cause. Patients with no documented death are censored at the last date they were known to be alive.
- The proportion (with 95% CI) of patients that experiences an event
- The median, range and 95% CI for time to development of an event.
- The proportion (with 95% CI) of patients treated with any treatment for RHDs recorded in the registry.

6.4 CORRELATION BETWEEN PATIENT CHARACTERISTICS AND PROGNOSIS

Multivariate Cox proportional hazards regression models will be used to identify variables that are important in predicting variables that predict are applied to correlate survival. These include clinical variables, but also the impact of various treatments received during the course of the disease.

6.5 INTERIM ANALYSIS

Interim (descriptive) analyses will be conducted when requested for the various sub studies, and at specific time points as decided or requested by the SC, but at least once a year. These analyses will report the patient and disease characteristics, treatment pathways and examine recruitment level across the different centres and countries. These analyses will allow an accurate statistical analytical plan to be developed including formal power calculation to determine the sample size necessary to examine important secondary endpoints, including the impact of the various therapeutic interventions reported in the Registry study.

7.DATA RECORDING AND DATA MANAGEMENT

7.1 DATA RECORDING

Data are recorded and entered through the web-based e-CRF at each national registry site and at clinical sites within each country or uploaded from National/European Registries by means of tailor made data transfer algorithms (if (re-)consent is required and adequate according to national regulations). A screening log is maintained at each site to ensure consecutive patient enrolment. All data collected for each patient are displayed in the patient data listings. History and clinical conditions are assessed from routine documentation and clinical evaluation performed in the context of inclusion and follow-up visits. The platform development and statistic unit is responsible for generation of queries.

7.2 DATA MANAGEMENT

The platform development and statistic unit is responsible for the Data Management. Thus, it is responsible for the import of data from the national/European registry sites and for the merging of all data in a central database. Procedures concerning data export, cleaning and database merging will be described in the Data Management Manual. Training will be provided for each site and a dedicated helpdesk will be available.

The EU general Data Protection Regulation provides every EU citizen with the ‘Right to be forgotten'. This might have implications for the data management. Procedures concerning the ‘Right to be forgotten’ will be described in the Manual of Procedures.

8. QUALITY CONTROL AND QUALITY ASSURANCE

The European Registry is a non-interventional study. Therefore, it is not considered necessary to conduct close monitoring activities with 100% source data verification for all patients. Instead, the quality of the data provided by the referral sites are evaluated on a sample of patients. This evaluation is conducted by the PM and the platform development and statistic unit.

In order to ensure source data verification, the participating centres must provide access to all relevant clinical records if applicable. Information concerning the identity of the patient does not leave the premises of the centre (see also 9.1 Subject identification and protection).

9.ETHICS

9.1 SUBJECT IDENTIFICATION AND PROTECTION

Patients are cared for according to their treating physician's best judgement. They are not being subjected to any experimental treatment or examination for the purposes of this study.

Personal data allowing patients' direct identification, as name and surname, national identity number or home address will not be received by ENROL. Instead, medical information will be received by ENROL along with a pseudonym generated by their medical doctors (at local level). The use of a pseudonymisation tool offered by the EU-RD Platform in the context of rare disease registries (https://eu-rd-platform.jrc.ec.europa.eu/_en) GDPR compliant is envisaged for this aim. The pseudonym is created at the local site and the link among the pseudonym and patients' identity is never transferred to ENROL. To avoid any doubt, the link among pseudonym and patients identity remains at local level and is not transferred to ENROL.

Pseudonymised medical information to be included in ENROL is the information gathered in the routine of medical care: date of birth, gender, diagnosis including genetics, blood parameters, clinical manifestations and therapeutic interventions. This information is strictly necessary for the achievement of ENROL aims, corresponding to a set of parameters defined at the European level as "Common data elements" to all Rare diseases registries, and a consensus of experts involved in ENROL team. As the registry evolves, data elements will be reviewed by the Steering Committee for assessing if an update shall be required.

ENROL will share patients' pseudonymised data with third parties under the implementation of the following appropriate safeguards to protect the data during and after the study:

Pseudonymised data held in ENROL will be shared to third parties (ie. researchers, patients' associations, policy makers, industry) in order to contribute to projects whose objectives are directly connected to improve healthcare provision for RHDs, thus connected to ENROL's aims. As previously indicated, ENROL gathers pseudonymized data, which means that information allowing the direct identification of the patient has not been transferred to the platform. Thus, the risk of re-identification is residual. Accordingly, and for the avoidance of any doubt, these third parties will never have access to the information that may directly lead to patients' identification.

Third parties interested in accessing data held by ENROL will be required to submit an application form that details the scientific purposes of the project for which the data is needed for its revision by ENROL Data Access Committee. Researchers may come from both public and private institutions in any country, including non-EU countries. All third parties will be required to sign legal agreements respecting the EU legislation and committing them to (i) use the data only for the purpose intended and authorized; (ii) not attempt to re-identification, including merging ENROL's data to other sources of data; and (iii) not contact the patient directly.

9.2 INFORMED CONSENT

ENROL policy has been established from the onset of the project aiming at establishing the legal frame for the setting up of a European Epidemiological platform ensuring safe sharing of patients' data in agreement with the Regulation (EU) 2016/679 of the European Parliament and the Council 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation). The General Data Protection Regulation supports the processing of personal data in the frame of registries in order to obtain high quality knowledge for the improvement of the quality of life for a number of people and improve the efficiency of health and social care services, providing that appropriate conditions and safeguards are set out in Union or Member State law.

RHDs patients' data will be collected from any EU Member State combining different sources of data, including Healthcare providers (ERN-EuroBloodNet members / Other EU healthcare providers) and EU/national/local existing registries. Accordingly, patients will be recruited at the national level in the patients' reference centers. The informed consent will be obtained if required by the national regulations by the physician in charge of the patient at the local level, and its obtention will be the responsibility of the local centre. An informed consent model has been developed taking into consideration General Data Protection Regulation requirements, and reviewed by the ERN-EuroBloodNet ePAGs, ensuring the inclusion of clarifications that may be been risen by the patients asked to understand and sign the consent.

Documented informed consent will be obtained for all patients before they are registered, if it is required by national regulation. If applies, all patients who are eligible for inclusion are informed of the aims and nature of the study and informed that all their clinical data will be treated confidentially, but that their medical records may be reviewed by authorized persons other than their treating physician for study purposes. Patients will be informed that participation is voluntary and that they can refuse participation at any time, without consequences for their further treatment.

The informed consent procedure will be performed in line with General Data Protection Regulation and in accordance with national and local regulatory requirements.

10. FINANCING

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http://www.eurobloodnet.eu/enrol/

https://ec.europa.eu/health/ern_en