Het Core Register

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Sponsor (in Dutch: verrichter/opdrachtgever)	***LUMC***
Subsidising party	***European Reference Networks for rare endocrine and bone disorders***

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ERN	**European Reference Network**
ENDO ERN	**European Reference Network for Rare Endocrine Diseases**
ERN BOND	**European Reference Network for Rare Bone Disorders**
EuRRECa	**European Registries for Rare Conditions**
EU	**European Union**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
IC	**Informed Consent**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Establishing a harmonised European Registry for Rare Bone and Endocrine conditions will dramatically change this lack of high-quality and comprehensive data. The registry has the capacity to better inform clinician-patient care decision making, facilitate epidemiologic mapping, accelerate research, expedite validation studies, benchmark clinical outcomes and provide leads for novel interventions.

The Core Registry collects a very small amount of information in a registry for a wide range of rare conditions including those that are covered within the European Networks of Health Care Providers for rare endocrine and rare bone conditions Endo-ERN and ERN-BOND. The data collected in the Registry will be used to improve clinical care as well as research. The registry can advise patients on suitable studies they can participate in and other registries. Patients that have been added to the registry and have given consent to access their own record can view their data and change their consent options.

INTRODUCTION AND RATIONALE

A core group of the European Reference Network on Rare Bone Diseases (ERN BOND) and Rare Endocrine Diseases (Endo-ERN) healthcare providers, patient representatives, Affiliated centers and other experts have joined their forces.
Establishing a harmonised European Registry for Rare Endocrine and Bone conditions will dramatically change this lack of high-quality and comprehensive data. The registry has the capacity to better inform clinician-patient care decision making, facilitate epidemiologic mapping, accelerate research, expedite validation studies, benchmark clinical outcomes and provide leads for novel interventions.

This project will establish and connect the corner stones of the already established registries EuRR-Bone and EURRECa and will

(1) a secure FAIR data infrastructure that can capture a core set of data for all patients and comprehensive data for a selection of diseases,

(2) the means to engage patients in data provision,

(3) the communication materials and efforts to connect healthcare providers and patients across Europe, and

(4) maintain the open infrastructure for local initiatives and disease-specific registries to connect.

The Core Registry is part of EURRECa and EuRR-Bone and collects a very small amount of information in a registry for a wide range of rare conditions including those that are covered within the European Networks of Health Care Providers for rare endocrine and rare bone conditions Endo-ERN and ERN-BOND.
The data collected in the Core Registry will be used to improve clinical care as well as research. The registry can advise patients on suitable studies they can participate in and other registries.
Furthermore the Core Registry allows the development of disease specific modules which are collecting a minimal disease specific dataset making harmonized datacollection throughout Europe available. To contribute to the registry HCP’s do not necessary have to be part of an ERN, any expert center can contribute to the registries.

OBJECTIVES

Data collection to evaluate the natural history on a variety of rare diseases represented by the ERN's.

STUDY DESIGN

Prospective observational data collection done by 2 platforms: e-REC and the Core Registry.

e-Reporting of Conditions (e-REC)

Electronic surveillance of the conditions that are covered by the ERN's are installed. Each contributor will be able to tailor his/her notifications to include only relevant age groups and conditions. The notifications data will be held in a dedicated database structured to facilitate analysis and reporting, and the system will provide a suite of extracts and reports for the purposes of data and statistical analysis. In order to encourage the timely completion of the data for the notified cases in the Core Registry, the system will issue e-REC IDs for use in the Core Registry automatically as soon as the contributor finalises a monthly notification.

This system has been active since 2018 and regular reports are put on the registries website: www.eurreb.eu.

The Core Registry

Has been developed since 2019 and has been adapted for EuRR-Bone in 2020. Details of the standard operating procedures are available at the registries websites. The design of the registry has been driven by security, incorporating both the needs of the clinical community and ethical oversight required on information governance. The platform provides various functionalities including querying, uploading/edit/deletion of cases and cross searching of cases. The registry platform allows data entry of sequential events and development of specific modules, such as what would be required for generic patient reported outcomes and for condition specific outcomes with specific availability of access for patients themselves. The development of the registry has drawn heavily on e-Science tools. A variety of security-supporting portal-based tools and advanced authorisation solutions have been utilized for this purpose. User and institute-oriented access control has been achieved through the Internet2 Shibboleth technologies (http://shibboleth.internet2.edu) which supports federated access control and delivery of digitally signed X509-based attribute certificates. These have been used for automatic configuration of portal contents, e.g. for restriction of access and usage of associated datasets according to the assigned user role within the portal. These technologies are constantly updated. Further facilities in the registry include the ability to bulk upload data and export data to approved investigators for analysis. Modules exist for access by specific users such as patients and enquire about their preferences. Again, it is anticipated that these functionalities will be simpler to develop and perform for a limited core data as opposed to a detailed disease registry. The bulk upload facility will prove helpful when uploading core data from existing disease registries to the Core Registry.

STUDY POPULATION

1.1 Population (base): All patients seen with Rare Bone and Endocrine conditions seen in the LUMC (adult and paediatric)

1.2 Inclusion criteria

All patients willing to participate

1.3 Exclusion criteria

none

1.4 Sample size calculation

Not Applicable

2. METHODS

2.1 Study parameters/endpoints

The data collection has been set up to follow the natural history of rare diseases.
A full dictionary of the core parameters currently assessed are found online. In addition each condition-specific module has a collection of data. Please find all our dictionaries online: https://eurreb.eu/registries/data-dictionaries/.
For more information on our condition-specific modules: https://eurreb.eu/registries/core-registry/condition-specific-modules/.

Group	#	Name	Description	Coding	Comment
1. Pseudonym	1.1.	Pseudonym	Patient's pseudonym	String	The JRC is working on providing a pseudonymisation tool to the registries (EUPID)
2. Personal information	2.1.	Date of birth	Patient's date of	Date (dd/mm/yyyy)	
	2.2.	Sex	Patient's sex at birth	• Female • Male • Undetermined • Foetus (Unknown)	
3. Patient Status	3.1.	Patient's status	Patient alive or dead	• Alive • Dead • Lost in follow-up	If dead then answer question 3.2
	3.2.	Date of death	Patient's date of death	Date (dd/mm/yyyy)	
4. Care pathway	4.1.	First contact with specialised centre	Date of first contact with specialised centre	Date (dd/mm/yyyy)	
5. Disease history	5.1.	Age at onset	Age at which symptoms/signs first appeared	• Antenatal • At birth • Date (dd/mm/yyyy) • Undetermined	
	5.2.	Age at diagnosis	Age at which diagnosis was made	• Antenatal • At birth • Date (dd/mm/yyyy) • Undetermined	

6 Diagnosis	6.1.	Diagnosis of the rare disease	Diagnosis retained By the specialised centre	Orpha code (strongly recommended – see link) / Alpha code/ ICD-9 code/ ICD-9-CM code / ICD-10 code	http://www.orphadata.org/cgi-bin/inc/product1.inc.php
	6.2.	Genetic diagnosis	Genetic diagnosis retained by the specialised centre	International classification of mutations (HGVS) (strongly recommended – see link) /HGNC/OMIM code	http://www.hgvs.org
	6.3	Undiagnosed case	How the undiagnosed case is defined	• Phenotype (HPO) • Genotype (HGVS)	
7. Research	7.1.	Agreement to be contacted for research purposes	Patient's permission exists for being contacted for research purposes	• YES • NO	
	7.2.	Consent to the reuse of data	Patient's consent exists for his/her data to be reused for other research purposes	• YES • NO	
	7.3.	Biological sample	Patient's biological sample available for research	• YES • NO	If YES answer question 7.4
	7.4.	Link to a biobank	Biological sample stored in a biobank	• YES (if appropriate use link)	https://directory.bbmri-eric.eu

8.Disability	8.1.	Classification of functioning/ disability	Patient's disability profile according to International Classification of Functioning and Disability (ICF)	• Disability profile / Score	http://www.who.int/classifications /icf/whodasii/en/

2.2 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences.

3. STATISTICAL ANALYSIS

Not applicable to the data collection.

4. ETHICAL CONSIDERATIONS

4.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (9th July 2018 see for the most recent version: www.wma.net).

4.2 Recruitment and consent

Patients will be asked to participate while visiting the outpatient clinic through the patient information forms which they can read and sign. If patients would also like to have access to the registries themselves, they consent for sharing their email to set up and account. Once patient have access to the registries, the consent is dynamic and patients can change their consent at will see figure below.

4.3 Benefits and risks assessment, group relatedness

As this is an observational study no risks are attached nor are there any direct benefits in the short term. Long-term benefits might include better care are ability to have access to their own data. Patients are active contributors to the registries, content wise but also governing wise. Patient representatives are present in all layers of the registries e.g. data-access committee, the various study groups.

5. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

5.1 Handling and storage of data and documents

The data of the Core Registry shall be held at the Leiden University Medical Center where the registries PI serves as a custodian of the data. The LUMC has a body of projects

associated with high-level security. In restricting access to the registry and its contents, roles based access control (RBAC) and identity based access control (IBAC) mechanisms are applied. The X509-based digitally signed roles (attribute certificates) shall be maintained in a secure attribute server. The Core Registry database proposes to use the (Open Source Registry System for Rare Diseases) OSSE software (https://www.osse-register.de/en/) which is increasingly used by several rare disease registries in Europe. No personal data except those mentioned above shall be stored on the Registry. All servers are backed up daily 30 days of backups are kept on a rotation Tivoli backup client runs on the SSD file servers and backs up any changes/new files every night. Volume Shadow Copy is active which runs twice daily at 07:00 then 12:00 - this allows roll back or restore a file to a specific point or day for a period of time. Access to the registries is set with a 2 factor identification requiring not only a password but onetime PIN as well.
All those involved in the running and development of the Registry will have to be up to date with Data Protection Regulations and will receive training as required by the LUMC.
The Endo-ERN and ERN BOND projects have received initial funding for 5 years followed by an bridging grant which runs to 2024, but it is anticipated that this funding by the EC will continue. The e-Reporting programme will continue for the life time of the ERN projects. The Core registry and its condition specific modules will last as long as there is an unmet need within the community. It is likely that the non-identifiable data that will collected will be stored for over 30 years in accordance with GDPR

5.2 Monitoring and Quality Assurance

Monitoring is done by the project management team in collaboration with the registries steering committee where once a month different items of the registries are subjected to a quality check. In addition, the project management team will perform a yearly quality week to oversee the more technical part of the registries, including checking active user accounts.
Quality assurance: Core Registry is designed to collect core information on a wide range of rare endocrine and bone conditions listed in the Conditions Dictionary below. The fields that are used to collect this core information include the core data elements that are recommended by European standards for data collection and a high proportion of them have universal identifiers. In addition, the Core Registry collects clinician and patient reported generic outcomes. Condition-specific outcomes can also be collected and have been developed for some conditions and can be developed for others.

To ensure high-quality data, high-quality insights and promote open science, the registry will adhere to the FAIR principles to facilitate data stewardship:

- Findable: (meta)data within the registries are unambiguously identifiable and described richly, i.e. stakeholders can find a unique reference to the registry via information about the registry. The registry will establish clear and accessible resources of data and metadata definitions, in machine readable formats, aligned with the European Rare Disease Registry Infrastructure (ERDRI) and the European Registry for Bone Conditions. It will be registered on the EU Rare Disease platform to ensure its metadata and data will be easily searchable and findable.
- Accessible: the registries will make its protocols for data communication, privacy preservation, authentication and authorization, available to optimize access to the registry content under defined conditions. In collaboration with the EJPRD, electronic access will be aligned with other initiatives, such that the registry can be efficiently used in conjunction with other knowledge recourses.
- Interoperable: Interoperability with other RD registries is ensured by the use of universal standard codes, such as Orphacodes and Logical Observation Identifiers Names and Codes (LOINC), IRDiRC recognized ontology standards such as the Human Phenotype Ontology (HPO), the ORPHANET rare diseases Ontology (ORDO),

and ontological models for the basic 16 data elements developed by JRC. This will be strengthened by the JRC initiative to develop a central ERN data dictionary. The content of the registries will thus be made linkable and machine readable, such that queries across multiple sources can be executed without additional work on making data compatible. The linking model that was developed for the JRC data elements in collaboration between VASCERN and the Leiden University Medical Center (LUMC) will provide a starting point for such queries. New definitions of outcomes and diseases will be published via journals and the registry's portal for human consumption, and ontologically modelled and entered into the JRC ERN data dictionary for use by machines. All formats will be computable and processable by common services for ERNs, as developed through the EJPRD project, JRC, and existing tools. (http://catalogue.rd-connect.eu/).

- Reusable: Conditions and other qualities for reuse will be defined in state-of-the-art machine-readable formats, such as data use licenses and consent codes (e.g. as defined by IRDiRC and the Global Alliance for Genomics and Health). Privacy of patients in data linking scenarios is ensured to the highest standards. Together with the promotion of standardized and harmonized data, this will ensure the possibility to reuse data under defined conditions, such as in combination with other data sources and registries, and to export reusable data in case of closure or extraction for downstream studies. Furthermore, the platform hosting the registry will be scalable, enabling the expansion of the Disease Specific Modules to more diseases.

These principles will promote proper collection, annotation, archival and long-term care of research data, with the goal that they become machine-actionable and reusable in downstream studies. In addition, these principles will allow third-party registries to align with the registry's design and link accordingly.

The guidelines pertain to biomedical data, but also to data access procedures encompassing the registries policies on data sharing, consent checking, privacy preserving record linkage, GDPR compliance, authorization and authentication. Where possible, the registries will follow IRDiRC recognized resources, and align with the EJPRD decisions regarding interoperability standards and alignment with global standards and emerging European infrastructure for rare diseases, such as in the Global Alliance for Genomics and Health, ELIXIR, BBMRI-ERIC, FAIR projects such as EOSC-Life, FAIRsFAIR, and FAIR4Health. ORDO/HPO, OMOP, HL7 FHIR, SNOMED CT, EMA WHO ATC, the FAIR data point specification, etcetera, will thus be assessed for appropriateness and how to best implement them for bone diseases. Implementation choices will be shared, such as via FAIRsharing.org and ERDRI.mdr.

Lastly the registries will implement Applications Programming Interfaces (API). This is to enable (and control) communication of information through computer programs/analysis tools, an Application Programming Interface (API) will be provided that supports FAIR principles. The FAIR data point specification will therefore serve as reference . The implementation of the API makes use of the registry's metadata descriptions to manage findability and accessibility, following and complementary to existing the registries data access protocols.

5.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

5.4 Annual progress report

Annual reports will be posted on the registries website: www.eurreb.eu.

5.5 Public disclosure and publication policy

Annual reports, all our policies, protocols and patient information sheets are publicized on the registries website: www.eurreb.eu.
The data shall be published as metadata and provided as reports to the members of Endo-ERN/ERN BOND and the EU and the data will be openly accessible on the Endo-ERN/ERN BOND website. These data will only show the frequency of encounters of each condition included within Endo-ERN/ERN BOND at the participating centres. If study groups would like to have access to the data they can request access via the data access committee via the data access request form (see also the registries webpages regarding obtaining registry data). The registries have a data access policy which is publicized on the website. See also: https://eurreb.eu/registries/obtaining-registry-data/

Please find the publications related to the registries on our website:
https://eurreb.eu/publications/

REFERENCES

Not applicable

We kindly refer to these websites:

www.eurreb.eu

www.eurr-bone.com