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# ERN BOND: The key European network leveraging diagnosis, research, and treatment for rare bone conditions

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ABSTRACT

There is no universally accepted definition for rare diseases: in Europe a disease is considered to be rare when affecting fewer than 1 in 2000 people. European Reference Networks (ERNs) have been the concrete response to address the unmet needs of rare disease patients and many pan-European issues in the field, reducing inequities, and significantly increasing accessibility to high-quality healthcare across Europe. ERNs are virtual networks, involving centres and patient representatives with the general scope to facilitate discussion on complex cases requiring highly specialised competences and trained expertise. ERN BOND - the European Reference Network on rare BONe Diseases - is one of these 24 approved networks with the specific ongoing mission to implement measures facilitating multidisciplinary, holistic, continuous, patient-centred, and participative care provision to patients, and supporting them in the full realisation of their fundamental human rights. ERN BOND includes in 2023 a total of 53 centres of expertise from 20 European countries. Its governing structure installed in March 2017 includes decision-making, operative and consultative committees, which comprise experts in the field and patient representatives ensuring patient's voice and perspectives are taken into account.

Over the years, ERN BOND has worked hard to achieve its mission and valuably contribute to the advancement of diagnosis, management, treatment, and research in rare diseases. The network activities are mainly related to (i) the provision of care which collectively involves averagely 2800 patients diagnosed per year, (ii) the development of education for and training of the healthcare personnel consisting until now in the realisation of 7 thematic workshops and 19 webinars, (iii) the dissemination and exchange and spread of knowledge via network's website (https://ernbond.eu/), social media channels, and newsletters, (iv) the management of related

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data through a disease registry currently mapping over 2300 cases and recording over 600 reported cases, and (v) the enhancement of research which now include two clinical trials endorsed by the network.

ERN BOND represents therefore an unprecedented move to improve the healthcare management of patients suffering from rare bone diseases through European collaborations. This network, through the support from the European Health Programme, will continue to pursue its efforts to achieve its goals, always maintaining the patients and their families at the centre of healthcare services.

## 1. Introduction

### 1.1. Rare diseases in Europe

There is no universally accepted definition for rare diseases (RDs) (Richter et al., 2015). We will refer here to the European Commission (EC) on Public Health's definition of RDs, which is "life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them" and occurring in "not more than five affected persons per ten thousand" (i.e. fewer than 1 in 2000 people) (Regulation (EC) 141/2000).

Although individually rare, RDs collectively impact a significant portion of the population; and it is estimated that, in Europe, about 30 million citizens are affected by one RD (Aartsma-Rus et al., 2021). This sheer number represents a major public health problem, and many challenges remain to be addressed in order to accelerate research and development of therapies, as well as to improve patient care. The majority of RDs are often associated with huge unmet needs due to the unavailability of standardised clinical practices and guidelines for diagnosis and treatment, as well as the necessity of a multidisciplinary approach. This is partially due to the paucity of research on RDs and to the lack of knowledge of such groups of diseases, especially at the primary care level, as very few universities have specific curricula for RD teaching (Tumiene et al., 2021).

### 1.2. European Reference Network on rare BONe Diseases

ERN BOND - the European Reference Network on rare BONe Diseases - is one of the 24 approved European Reference Networks (ERNs), which was set up in March 2017 under the Directive 2011/24/EU on the application of patients' rights in cross-border healthcare where the EC has recognized these unmet long-term needs of RD patients. The specific ongoing mission of ERN BOND is to implement measures facilitating multidisciplinary, holistic, continuous, patient-centred, and participative care provision to people living with rare bone diseases (RBDs), and supporting them in the full realisation of their fundamental human rights.

The aim of this manuscript is to describe how ERN BOND has been set-up and how this unique initiative contributed to improve the healthcare of patients with RBDs and complex conditions through European collaboration, bringing swift interchange of information, expertise, and practice to shorten time to diagnosis, and improve management and treatment, and supporting RBD patients and their families by illustrating the results obtained so far.

## 2. Methods

### 2.1. ERN BOND disease coverage

RBDs represent about 10% of the known RDs. The ERN BOND scope of action concerns two main RBD categories: skeletal dysplasias and metabolic bone-related conditions, comprising all rare diseases (essentially congenital, chronic, and of genetic origin) affecting cartilage, bone, and dentine. Currently, there are 771 different RBDs associated with 552 genes, classified into 41 groups based on their clinical, radiographic, and/or molecular phenotypes, as described in the 11th version of the Nosology of Genetic Skeletal Disorders which was based on the previous work on the 2019 Nosology carried out within the joint collaboration between ISDS – the International Skeletal Dysplasia Society, ERN BOND and Orphanet, the portal for RDs and orphan drugs (Unger et al., 2023) (Mortier et al., 2019).

During the first years of its existence, ERN BOND prioritized three major diseases as pilot conditions: Achondroplasia (ACH), Osteogenesis Imperfecta (OI) and X-linked hypophosphatemia (XLH), selected on the basis of their disease prevalence, severity, diagnostic and management difficulties, treatment availability, and novel emergent therapies. ERN BOND is now expanding its focus to other RBDs, including ultra-rare bone disorders, replicating the best practice methodology and effective systematic approaches obtained from the pilot conditions, thereby leading to improvements in the quality and effectiveness of care in all

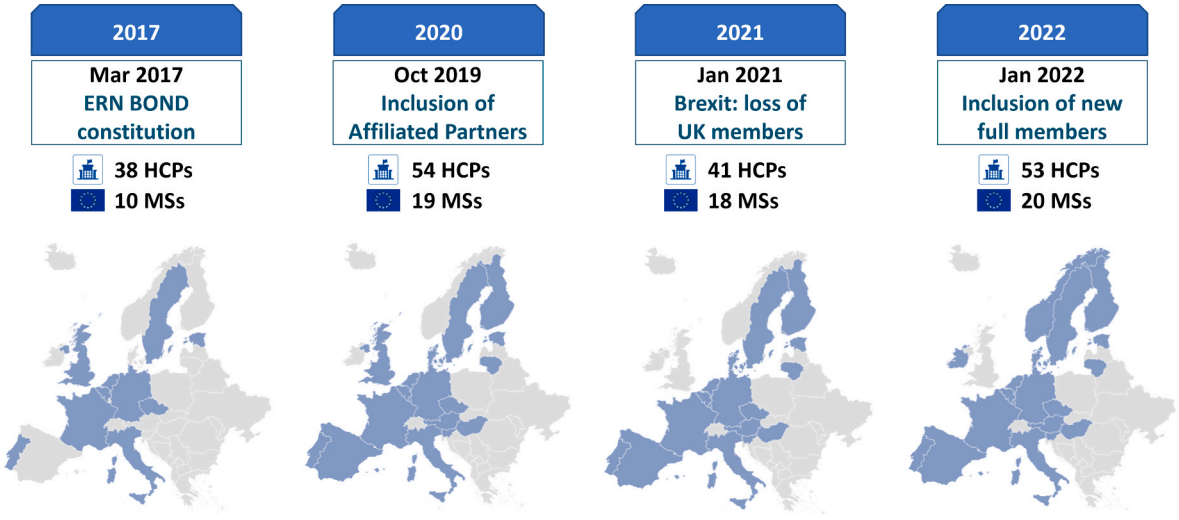
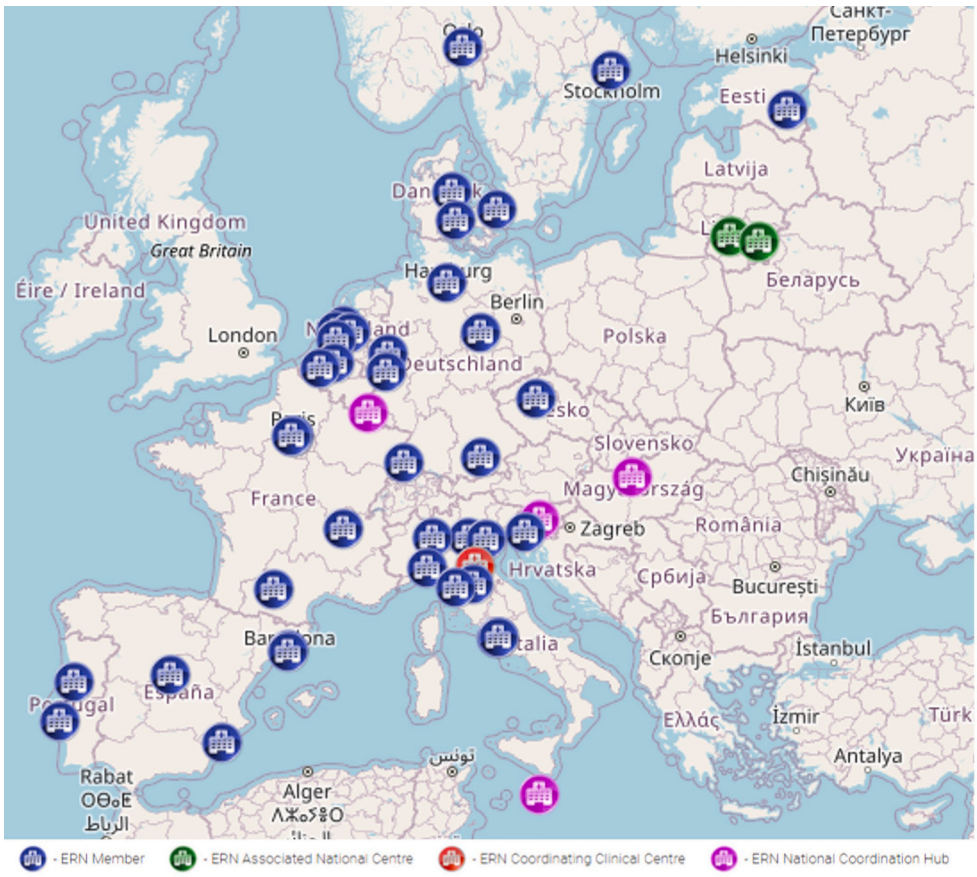



**Fig. 1.** ERN BOND evolution in terms of membership and geographical coverage (2023).
Legend: HCPs = HealthCare Providers; MSs = Member States; UK= United Kingdom.




ERN BOND
EUROPEAN REFERENCE NETWORK ON RARE BONE DISEASES

| Country | No. of HCPs |
|---|---|
| Austria | 1 |
| Belgium | 2 |
| Czech Republic | 1 |
| Denmark | 3 |
| Estonia | 1 |
| Finland | 1 |
| France | 6 |
| Germany | 8 |
| Hungary | 1 |
| Ireland | 1 |
| Italy | 11 |
| Lithuania | 2 |
| Luxembourg | 1 |
| Malta | 1 |
| Netherlands | 4 |
| Norway | 1 |
| Portugal | 2 |
| Slovenia | 1 |
| Spain | 4 |
| Sweden | 1 |

Source: EC website on ERNs

**Fig. 2.** Number of ERN BOND HCPs per MSs (2023).

RBDs.

### 2.2. ERN BOND composition, membership, and geographical coverage

In 2017 ERN BOND consisted of a network of 38 founding Health-Care Providers (HCPs), i.e., centres of expertise in the scope of the network, located in 10 Member States (MSs): Belgium, Czech Republic, Estonia, France, Germany, Italy, The Netherlands, Portugal, Sweden and United Kingdom (UK). HCPs participating in the specific call and fulfilling the admission criteria of the Directive 2011/24/EU were accepted to become part of the ERN as full members. Admission criteria were defined in the call and included the HCP self-assessment on the area of

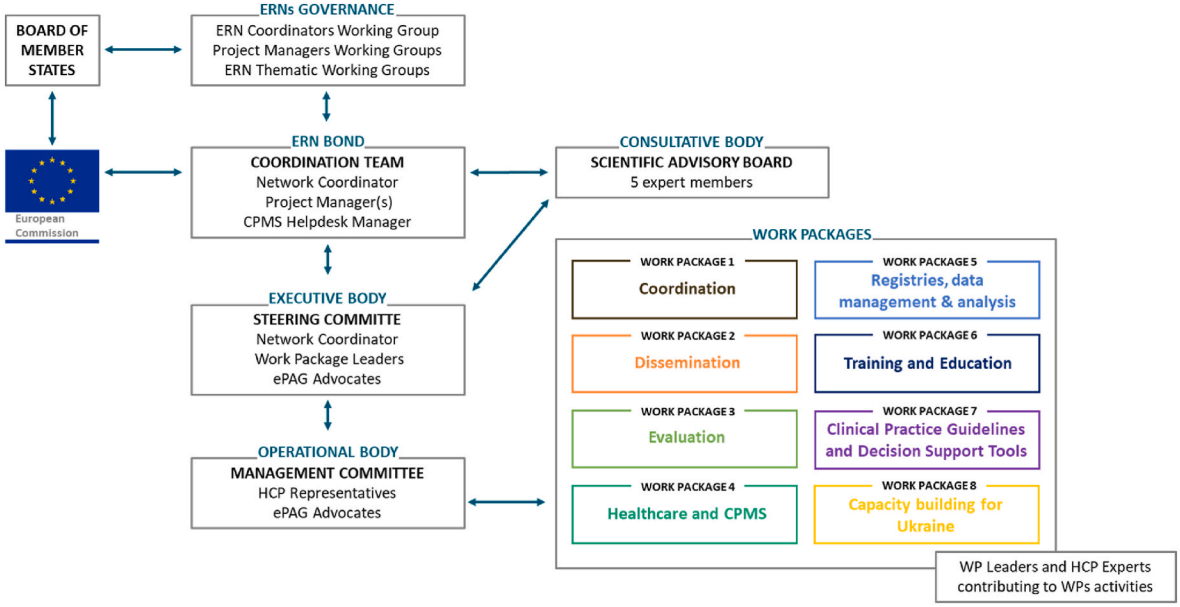



**Fig. 3.** ERN BOND governing structure.

expertise, the service provided as well as their organisation, including their multidisciplinary structure. Additionally, the self-assessment application had to be accompanied by the official endorsement by their relevant MS (ERNs overview). Several changes occurred since, both in terms of network size and geographical coverage. In 2019, 16 Affiliated Partners (i.e., HCPs in a MS not at the time represented in an ERN) were incorporated to ERN BOND following the relevant Commission Implementing Decision (EU) 2019/1269 with the aim of increasing the accessibility and achieving a whole EU and European Economic Area coverage, adding thus Austria, Denmark, Finland, Hungary, Lithuania, Luxembourg, Malta, Slovenia and Spain as MSs.

At the end of 2020, 13 UK members terminated their BOND membership due to Brexit but, in 2022, ERN BOND gained both in size (number of MSs and HCPs) and disease coverage by acquiring 22 new full members (9 of which being already Affiliated Partners), adding further to the BOND map Ireland and Norway. New full members were admitted through the specific call for new HCPs to join existing ERNs, launched by the EC.

To date, ERN BOND includes a total of 53 HCPs and their specialist departments in RBDs from 20 European MSs, including 47 Full Member HCPs, 6 Affiliated Partners (2 Associated National Centres and 4 National Coordination Hubs). Fig. 1 shows the ERN BOND evolution in terms of membership and geographical coverage, and Fig. 2 shows the number of HCPs per MSs.

### 2.3. ERN BOND governance structure

ERN BOND has installed its governing structure at its inception in March 2017, which has been recently updated in September 2023 (Fig. 3). Unlike some other ERNs, the ERN BOND governing structure is activity-oriented instead of disease-oriented due to the peculiarities of RBDs. Indeed, RBD patients share common special needs. Moreover, these disorders have a significant clinical overlapping and a considerable number of groups leading to a continuous updating of the clinical classifications (just consider that since 1970 eleven revisions of RBD classifications have been released) which makes their division in subcategories very difficult (Unger et al., 2023).

ERN BOND activities transversally address RBDs and have been then adapted and implemented over time through thematic Work Packages (WPs) focusing on the following thematic areas to respond to the EC requirements/indications: network coordination, dissemination and evaluation, guidelines, disease registry, diagnosis, research, and education and training. Each WP is composed of its leaders, managing and coordinating the respective scientific activities, of clinical and scientific experts working in ERN BOND HCPs and of representatives of ePAGs (the European Patient Advocacy Groups working in the ERNs), synergistically collaborating towards achieving the network's goals.

The network coordination includes the Coordinator, who supervises the overall progress of all network activities and also acts as intermediary between the ERNs governance bodies, the EC and other ERNs, and the Coordination Team, which carries out the day-to-day operational activities, as well as supports network members.

All WP leaders and two ePAG representatives are part of the Steering Committee, the decision-making body, chaired by the Coordinator. ePAG representatives' presence in the ERN BOND activities and in the governing bodies ensures that the patient's perspective is always heard within the network.

The Management Committee, the operational body, comprises of one representative per HCP full member and all ePAG representatives (ERN BOND ePAGs).

Finally, ERN BOND can also rely on the Scientific Advisory Board, which is the consultative body, providing scientific advice to the network regarding ongoing and upcoming priorities. Board members are experts in different areas, covering clinical research, diagnostic, ethical, legal and social implications, ontologies, and patients' representatives. They are nominated through voting by the Management and Steering Committee members.

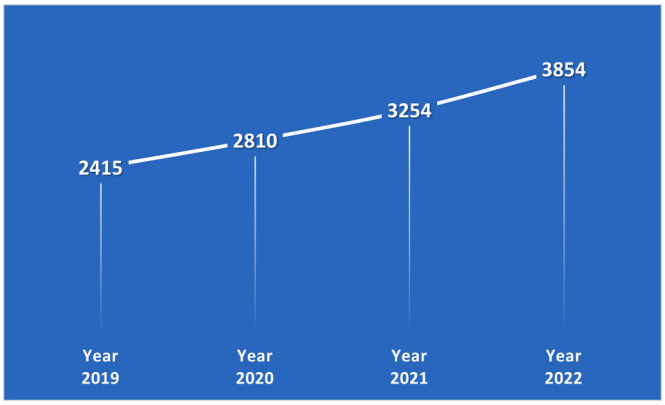



**Fig. 4.** Number of new patients referred per year to the ERN BOND centres.

As better illustrated hereunder, the inclusion of ePAGs into ERN BOND's governance from the start has been an added value to network activities and achievements, which intrinsically contain the patients' perspective.

### 2.4. ERN BOND and patients' representatives

ERN BOND's uniqueness dwells also in the actions implemented for RD-Patient engagement. In fact, the Patient voice is represented in ERN BOND by ePAGs which have been established by EURORDIS – a non-profit alliance of over 1000 rare European disease patient organisations – to support patient participation in ERNs decision-making processes ensuring a democratic process of patient representation.

ERN BOND's mission and vision are thus very much patient-centred. Indeed, ePAG advocates have been part of the network right from the outset including contributions to the preliminary phases of the network constitution, anticipating the following admission criterion to be fulfilled in order to become an ERN partner or coordinator (cfr. General Criteria and Conditions, Commission delegated decision; 2014/286/EU). ePAGs form therefore a structural part of the network's governing bodies and all WPs, ensuring that patients' valuable perspectives are taken into account before any decision-making.

The ePAG inclusion in ERN BOND is voluntary and is subject to a self-candidature accompanied by an endorsement letter from their Patient Organization, and to the fulfilment of the admission criteria stated in the "Network agreement regarding the rules for the European patient advocacy groups" (ERN BOND ePAGs). The ePAG representation in ERN BOND has grown with time, from 2 to 7 representatives; this increasing the overall representation, disease coverage, diversity and guidance, following the network procedure. The ePAG representatives currently represent the following diseases: Achondroplasia, Osteogenesis Imperfecta, X-linked Hypophosphatemia, Fibrodysplasia Ossificans Progressiva, Multiple Osteochondromas, Ollier disease and Maffucci syndrome. As the patient involvement is crucial to this network, ERN BOND also collaborates through its members with many other national and international RD-patient organisations.

## 3. Results

Over the years, ERN BOND has worked hard to achieve its mission and valuably contribute to the ERNs general goal of advancement in diagnosis, management, treatment, and research in RBDs.

The ERN BOND website, social media channels, and regular newsletters detail all time after time planned and implemented ERN BOND activities. As previously anticipated, along with the project management and network performance monitoring, the network activities are mainly related to the provision of care to RBD patients, and the development of

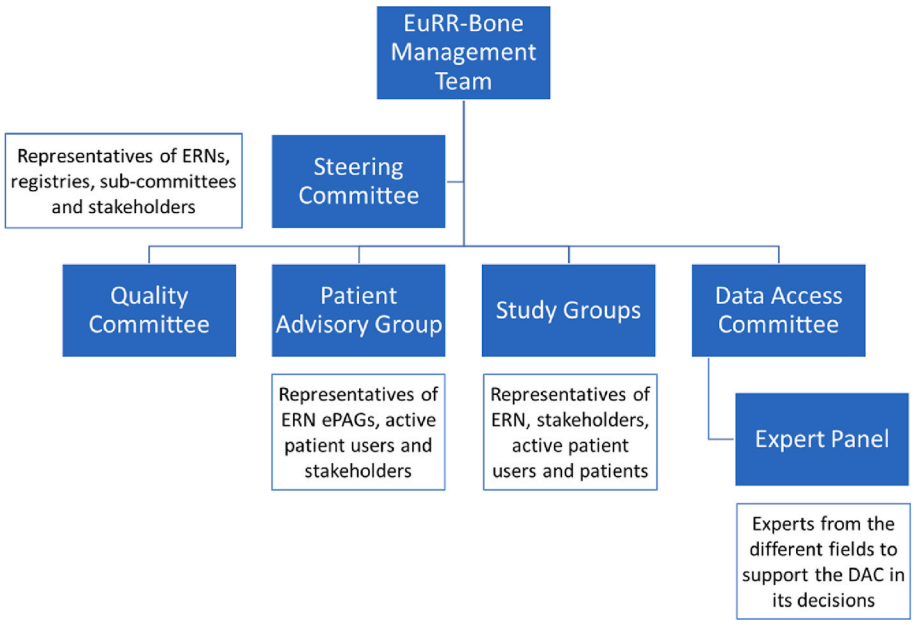



**Fig. 5.** EuRR-Bone governance structure in 2023
Legend: DAC = Data Access Committee; ePAGs = European Patient Advocacy Groups.

education and training for the healthcare personnel involved in RBD management, the dissemination, the exchange and spread of knowledge, the management of RBD data through disease registries, and the enhancement of research and clinical trials activities.

### 3.1. Provision of care to RBDs patients

The ERN BOND HCPs deliver the overall expert care needed for 2800 patients diagnosed on average per year. The number of new patients referred to the ERN BOND centres with the diagnosis of a disease or condition within the scope of the network has increased from 2415 patients in 2019 to 3851 in 2022 (Fig. 4).

Along with the direct provision of care by the HCPs, the network experts participate and contribute to the virtual multidisciplinary discussions on the ERN BOND CPMS (Clinical Patient Management System), the web-based platform for ERNs created to facilitate the interaction between clinicians dealing with RDs.

A devoted ERN BOND Operational Helpdesk has been activated in October 2018 for assisting users in the use of the platform. ERN BOND has made significant strides in utilizing the CPMS by the creation of over 50 case virtual discussions dedicated to the collaborative management of RBD patients. These discussions are strategically designed to address specific aspects of patient care, with a focus on diagnosis, treatment, a combination of both or other needs demonstrating a comprehensive approach and reflecting the multidisciplinary nature of the network.

### 3.2. Pathways, guidelines and best practices for RBDs

Considering that evidence-based clinical guidelines are fundamental for the development of high-level care pathways, the network has taken steps earlier on for the development of specific RBDs clinical care pathways, with a view to facilitate and improve the diagnosis of RBDs, first focusing on OI. This resulted in the "ERN BOND White Paper on the Diagnosis of Osteogenesis Imperfecta" that provided a state-of-the-art picture of the common challenges encountered in diagnosing OI.

Along with this priority to meet an unmet need, and in line with the aim of disseminating knowledge about RBDs, the network also has endorsed clinical care pathways, guidelines and best practices recommendations for the diagnosis and management of RBDs that have been developed and authored by the network members (ERN BOND Guidelines).

In addition, in a pilot study, in-house and national clinical practice guidelines for the diagnosis, treatment and follow-up of OI and ACH have been collected and then translated into English. This study is still ongoing to allow the inclusion of guidelines from BOND's new HCPs and MSs. The complete set of guidelines currently used by HCPs from all MSs represented in BOND will be analysed for similarities, differences and up-to-date status in order to determine the state of update and need for cross-border harmonisation of best clinical practice guidelines across MSs. ERN BOND has also been recently selected by the ERN Guideline Programme, which is promoted and funded by the EC, for support with the ERN BOND focused project to develop clinical decision tools for the management of pregnancy in OI, addressing one of the unmet needs identified by the ERN BOND ePAGs. This support will be provided by specialised methodologists and information specialists from the Health Technology Assessment Agencies of the Consortium of the ERN Guidelines Programme (OSTEBA - BIOEF).

### 3.3. Review of Orphanet classification of RBDs

The harmonisation activities also include a collaboration between ISDS, ERN BOND and Orphanet for the revision and update of the classification of RBDs in the Orphanet database. This ongoing activity facilitates disease identification, early diagnosis and management of these disorders, thus contributing to improvement in quality of life and better treatment outcome.

### 3.4. Education and training programme

ERN BOND has contributed to the exchange and dissemination of existing knowledge on RBDs by implementing several activities and developing a specific education and training programme. This programme addresses different aspects of topics related to RBDs and more broadly RDs in general, consisting until now in the realisation of seven thematic workshops and 19 webinars.

Thematic workshops consist of stand-alone workshops or sessions included into disease specific congresses, scientific societies meetings, or events promoted by RBD patient organisations, in order to spread knowledge on RBDs among a very large number of disease-experienced (and non-expert) healthcare professionals all over the world (ERN BOND

Thematic workshops).

Although they are generally conducted in English, some webinars have been performed live in the national language of speakers and panellists with English subtitles added to the online recording. Webinars are advertised among the ERN BOND community through a dedicated newsletter and to the wider community through the website and social media channels.

Some e-products have been jointly produced with other RD societies in line with the collaborative spirit promoted by the EC. In particular, a Webinar Series on Rare Bone Diseases was organised in 2023 with the European Calcified Tissue Society (ECTS); a collaboration with the European Joint Programme on Rare Diseases (EJP RD) and the European Rare Disease Research Coordination and Support Action (ERICA) is in place for their webinars on RD clinical trials (ERN BOND webinars).

Along with the realisation of the education and training programme on RBDs, activities are ongoing for identifying and assessing the challenges and gaps in education and training in Rare Bone & Mineral Diseases within BOND's MSs as baseline for realising a comprehensive hybrid Education Programme in Rare Bone & Mineral Diseases, which will substantially contribute in filling the gap in specific academic curricula regarding RBD teaching.

### 3.5. Registries

EuRR-Bone is the European Registries for Bone and Mineral Conditions which was created in April 2020. It has its own governance structure, which includes its steering committee and data access committee (Fig. 5).

EuRR-Bone is composed of 2 registries: the e-reporting platform (e-REC) and the Core Registry with disease specific modules. It shares its platform with the European Registries for Rare Endocrine Conditions (EuRRECa) to reduce double entries with overlapping bone and mineral conditions between ERNs.

e-REC is an electronic reporting system which captures new patient activity in HCPs. It was designed to support the ERNs in their continuous monitoring program and allows for a better understanding of the occurrence of the rare conditions covered within the network and is currently counting 2376 cases from 57 centres from 20 worldwide countries.

The EuRR-Bone Core Registry is a registry dedicated to the collection of core data elements on all patients with a wide range of rare bone and mineral conditions; it can also collect generic, disease specific, clinician and Patient-Reported Outcomes (e.g., quality of life, pain, etc.), some of which designed by the patient representatives of the modules. The Core Registry is open for data entry by clinicians and by patients as it has a patient facing platform. It is now used by 20 centres in 13 countries, and 601 cases have had been reported so far. To date, six disease-specific modules have been drafted by ERN BOND experts within the EuRR-Bone Core-Registry:

- Pseudohypoparathyroidism/Inactivating PTH/PTHrP signaling disorders, released in 2022 in collaboration with EuRRECa
- Achondroplasia, released in February 2022
- Fibrous Dysplasia/McCune Albright syndrome, released in April 2022
- Osteogenesis Imperfecta, released in July 2022
- Rare Hypophosphatemia, released in January 2022
- Melorheostosis, released in 2023 in collaboration with ECTS
- Parathyroid carcinoma, released in 2023 in collaboration with EuRRECa

The EuRR-Bone project was sustained by a specific grant specifically devoted to the establishment of ERN disease registries under the European Union's Health Programme (2014-2020) and is now under the same ERN BOND grant. The original EuRR-Bone proposal was built on the outcomes of two surveys conducted by ERN BOND Working Group in 2019 (Javaid et al., 2021) (Priego Zurita et al., 2023). All reports, data dictionaries as well as ethical approvals are posted on the registries website, facilitating members to start reporting. The EuRR-Bone management team holds 2 monthly open online training sessions to support the entrance of new centres or discuss potential projects with active members (EuRR-Bone training sessions).

### 3.6. Research and clinical trials

Although research is not the principal scope of ERNs, ERN BOND took some actions in order to facilitate research and clinical trials among members. The establishment of multicentred research projects and/or clinical trials is still very challenging as it presents several ethical, legal, and social implications among the different national regulatory boards. However, two clinical trials, under EU projects, are currently endorsed by ERN BOND and conducted by network members. Firstly, MCDS-Therapy, an open label phase I/II trial repurposing Carbamazepine for the treatment of children with Metaphyseal Chondrodysplasia, Schmid type, and MOI-A study, a matrix-directed therapy in older adolescents and adults with OI, within the REMEDi4ALL project.

### 3.7. Emergency situations

ERN BOND during its lifetime had to face the two worldwide emergency situations: the COVID-19 pandemic and the war in Ukraine. In these extraordinary scenarios, ERN BOND concentrated its effort in setting up and participating in initiatives aimed at supporting both patients and their families and healthcare professionals in dealing with RBDs.

From the beginning of the COVID-19 pandemic in Europe, ERN BOND members started several initiatives. In particular, a COVID-19 emergency webpage has been created by ERN BOND to become a hub for the RBD community, including a list of COVID-19 guidelines and recommendations produced worldwide that have been collected and made available for consultation (ERN BOND COVID-19 section). In addition, a unique initiative among ERNs and RDs community has been implemented by setting up the "COVID-19 Helpline for Rare Bone Diseases", a direct and dedicated 24/7 telephone line for RBD patients and clinicians in the intensive care units and/or COVID-19 wards treating COVID-19 patients affected by RBDs, in particular OI patients (Sangiorgi et al., 2021).

This successful experience launched in Italy gave the possibility to highlight the fundamental role of remote high quality of care for RBDs during the COVID-19 outbreak that could become a gold-standard practice for remote care, particularly relevant for RBD patients (Brizola et al., 2020). Along with these actions, ERN BOND organised and/or contributed to 7 webinars on COVID-19 and RDs related topics.

In the case of the Ukrainian situation, ERN BOND has adhered to the ERNs' initiative to build the Rare Diseases Hub Ukraine to provide all Ukrainian RD patients with specialised medical support they may need during this emergency by connecting them with relevant organisations and hospitals. In particular, ERN BOND, in collaboration with the Rare Diseases Hub Ukraine, successfully organised multidisciplinary visits for Ukrainian refugees affected by RBDs and provided support to healthcare professionals for the treatment of their RBD patients located in Ukraine.

## 4. Discussion

Although the management of RDs still represents a major challenge, the ERNs initiative represents an unprecedented move to improve the healthcare management of patients suffering from RDs and complex conditions through European collaborations. During the last 6 years of activity, ERN BOND has brought together healthcare professionals, researchers, patient representatives, and other crucial stakeholders, to join forces and collaborate towards the multidisciplinary, holistic, continuous, patient-centred and participative care of patients and their

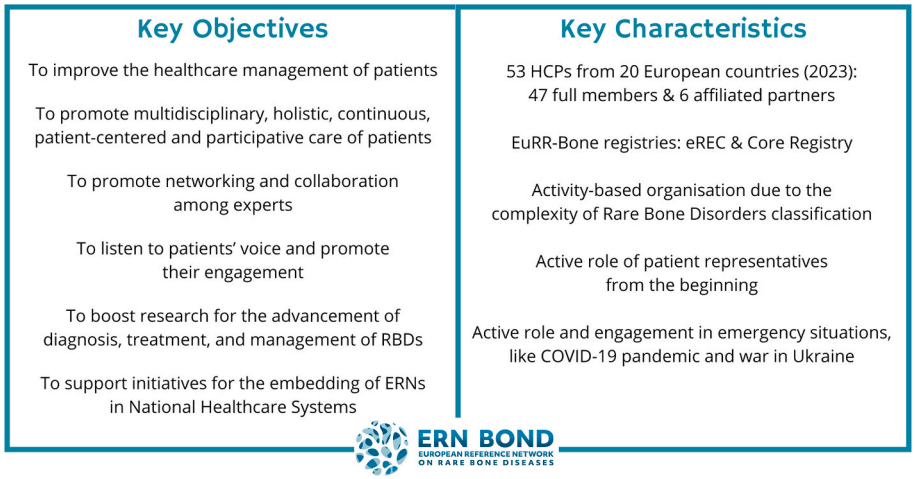



**Fig. 6.** ERN BOND key objectives and peculiarities
Legend: HCPs = HealthCare Providers; ePAGs = European Patient Advocacy Groups.

families living with RBDs (Fig. 6). In the coming years, ERN BOND will continue, thanks to the EU support from the Health Programme (EU4Health Programme 2021–2027), to pursue its efforts to achieve its goals facilitating full access to highly specialised healthcare for all RBD patients across Europe, to promote research for the advancement of diagnosis, treatment, and management in these diseases, and to exchange knowledge among experts in the field, always maintaining RBD patients and their families at the centre of healthcare services. In particular, ERN BOND will contribute and support the currently underway initiatives for the embedding of ERNs into national networks endorsed and sustained by the respective National Healthcare authorities. In this regard, ERN BOND has already formalised its Italian Network on RBDs obtaining the endorsement of the national healthcare authorities.

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## CRediT authorship contribution statement

**Lorena Casareto:** Conceptualization, Data curation, Project administration, Writing – original draft, Writing – review & editing. **Natasha M. Appelman-Dijkstra:** Validation, Writing – original draft, Writing – review & editing. **Maria Luisa Brandi:** Validation, Writing – original draft. **Roland Chapurlat:** Validation. **Valérie Cormier-Daire:** Formal analysis, Validation, Writing – original draft. **Neveen A.T. Hamdy:** Writing – original draft, Writing – review & editing. **Karen E. Heath:** Writing – original draft, Writing – review & editing. **Joachim Horn:** Formal analysis, Validation, Writing – original draft. **Giovanna Mantovani:** Validation, Writing – original draft, Writing – review & editing. **Klaus Mohnike:** Validation. **Sérgio Bernardo Sousa:** Validation, Writing – original draft. **André Travessa:** Formal analysis, Validation. **Lena Lande Wekre:** Validation, Writing – original draft. **M. Carola Zillikens:** Writing – original draft, Writing – review & editing. **Luca Sangiorgi:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

## Data availability

Data will be made available on request.

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