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EDITORIAL

Clinical practice guidelines: the first year of activity of the European Reference Network on Rare and Complex Connective Tissue and Musculoskeletal Diseases (ERN ReCONNET)

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INTRODUCTION

An impressive number of almost 5000–8000 rare diseases affect the daily lives of around 30 million people in the European Union (EU) and many of those affected by a rare or complex condition do not have access to diagnosis and high-quality treatment.

European Reference Networks (ERNs) are virtual networks involving healthcare providers (HCPs) across Europe with the aim to tackle complex or rare diseases and conditions that require highly specialised treatment and a concentration of knowledge and resources. ERNs offer the potential to give patients and doctors across the EU access to the best expertise and timely exchange of life-saving knowledge, making knowledge travel more than patients.¹

Following the first call for proposals in July 2016, the first ERNs were approved in December 2016 and launched in March 2017 in Vilnius during the 3rd conference on ERNs, where their kick off meetings took place. At their inception, the networks comprised more than 900 highly specialised healthcare units located in 313 hospitals in 26 EU countries.² From this date, the 24 ERNs are working on a range of thematic issues, including rare connective tissue diseases, bone disorders, childhood cancer, metabolic disorders and immunodeficiency.

To achieve ERN status, network members applied to a Call from the European Commission. This application was assessed by an Independent Assessment Body which completed reports on each applicant. The Board of Member States then decided whether or not

Key messages

What is already known about this subject?

- ▶ Clinical practice guidelines (CPGs) can guide clinicians on how to treat patients and offer a possible support to optimise the diagnostic/therapeutic process in a difficult field.
- ▶ CPGs are designed to support the decision-making processes in patient care and their content is based on systematic reviews of clinical evidence, the main source for evidence-based care.

What does this study add?

- ▶ This work is dedicated to the identification of existing CPGs in the field of rare and complex diseases and to the identification of physicians and patients unmet needs.
- ▶ This is the preparatory work to define a strategy of implementation of existing CPGs and/or development of new CPGs.

How might this impact on clinical practice?

- ▶ The implementation and development of new CPGs will support the harmonization of care in rare and complex connective tissue diseases in line with the mission of the European Reference Network ReCONNET.

to approve an ERN application, and it was based on the main key criteria, represented by: patient-centred and clinically led, the engagement of at least 10 members in at least eight countries, a strong independent assessment, the fulfilment of Network and member criteria, the endorsement and approval by national authorities. Over the next 5 years, ERNs are expected to reinforce their capacities to benefit thousands of EU patients suffering from a rare or complex condition; moreover,

many of the ERN initiative receives support from several EU funding programmes, including Horizon 2020, the Health Programme and the Connecting Europe Facility.

The ERN ReCONNET (European Reference Network on Rare and Complex Connective Tissue and Musculoskeletal Diseases)³ is the ERN aimed at improving the management of Rare Connective Tissue and Musculoskeletal Diseases across the EU. The ERN ReCONNET, involves 26 HCPs, from eight different EU countries: Belgium, France, Germany, Italy, Netherlands, Portugal, Romania and Slovenia. Of note, the contribution is on a voluntary basis. The Network covers the following 10 rare and complex connective tissue diseases, which were identified based on the epidemiology of the diseases (any disease affecting fewer than 5 people in 10 000 is a rare disease) and suggestion of the steering committee members (for complex diseases: systemic lupus erythematosus and Sjögren's syndrome): systemic sclerosis, mixed connective tissue diseases, idiopathic inflammatory myopathies, antiphospholipid syndrome, undifferentiated connective tissue diseases, IgG4-related diseases, relapsing polychondritis, systemic lupus erythematosus, Sjögren's syndrome, Ehlers Danlos syndromes.³

One of the most relevant added value of the ERN ReCONNET is the involvement of Patients' Representatives within all the activities of the Network. In fact, an intense collaboration has been established with the ERN ReCONNET European Patient Advocacy Group (ePAGs). Their role is to provide patients' opinion and input in the activities of the 10 work packages (WPs), to give the opinion and views of the patient groups, to collaborate in the evaluation of how the ERN acts on feedback from patients, to review the performance of the ERN & contributing to research, to promote and encourage a patient-centric approach, to develop and disseminate patients' information, to ensure that patient rights and choices are taken into account in decision-making and to identify relevant national patients' organisations to work with the ERN's HCPs.

CLINICAL PRACTICE GUIDELINES

Clinical practice guidelines serve as a great equaliser in the field of rare diseases: as a matter of fact, they can mean the difference between no care/substandard care and patients living longer, healthier lives with fewer complications. Guidelines, whether designed to support correct and early diagnosis or care, can serve as a blueprint of excellence, to advise clinicians (general practitioners and specialists) on how to treat patients in a way that reflects the best possible updated knowledge and therefore generating the best possible outcomes. Clinical practice guidelines are not fixed protocols that must be followed but are intended for healthcare professionals and providers to be considered as a possible support to optimise their diagnostic/therapeutic process in a difficult field.

Additionally, since the Network wishes to be as inclusive as possible, other HCPs, after approval of the Steering Committee, but not officially involved in the ERN ReCONNET joined the work on Clinical Practice Guidelines.

The ePAGs Representatives have intensely collaborated to the project, organising and participating to regular web conferences, providing their input into the WPs and participating to different meetings. Moreover, the input of the ePAGs Representatives was particularly important in WP3, where they actively contributed to the preparation of the final manuscripts realising a specific paragraph on patients' unmet needs on Clinical Practice Guidelines.

The whole work of WP3 was based on the eminent definition of the Institute of Medicine according which Clinical Practice Guidelines are 'statements that include recommendations, intended to optimise patient care, that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options'.⁴

Before planning the development of any potential new Clinical Practice Guidelines, the first-year activities of the network aimed at assessing the state of the art' on Clinical Practice Guidelines available for rare and complex Connective Tissue Diseases. The work has been made by conducting systematic literature reviews (SLRs) and through the recognition of official documents from scientific societies about Clinical Practice Guidelines for the different subgroups of rare and complex Connective Tissue Diseases.

Specifically, the overall activities had been subdivided in five steps:

Step 1—Identification of existing guidelines. A SLR based on controlled terms (MeSH and Emtree) and keywords of the diseases and publication type (guidelines) was performed on Medline (Pubmed) and Embase databases without specific temporal limits. Moreover, in order to implement the list of guidelines provided, each disease group performed a hand search of further relevant documents.

Step 2—Discussion on the existing guidelines. In order to create a starting point to discuss among each disease group, the experts evaluated Clinical Practice Guidelines following the AGREE II tool checklist (an international tool to assess the quality and reporting of Clinical Practice Guidelines) which was used only as guidance, not for formal appraisal. At this stage, a formal methodological evaluation with the AGREE II tool was not performed, since such an activity is already planned for the 2-year activities on WP3 also in the perspective of an eventual adaptation of the, existing guidelines. Each disease group organised more than one web meeting in order to check the work status and to follow the discussion performed in each group, including different members of different EU countries, perfectly fulfilling the rationale of the planned activities for WP3 and the real spirit of the ERNs.

Step 3—Preliminary report on guidelines assessment. During the ERN ReCONNET meeting on 5 November 2017 in San Diego (ACR 2017), each disease group Representative presented a preliminary report on the assessment performed and preliminary considerations on potential gaps on existing Clinical Practice Guidelines.

Step 4—State of the art on CPGs. A state of the art on Clinical Practice Guidelines has been performed for each disease covered by the ERN ReCONNET and is presented in the articles included in the present supplement together with the results of the *Step 5—Identification of unmet needs.*

The literature review has highlighted the existence of partially sufficient Clinical Practice Guidelines for some rare and complex Connective Tissue Diseases (Systemic Lupus Erythematosus, Idiopathic Inflammatory Myopathies, Systemic Sclerosis, Sjögren Syndrome), while demonstrating the absence of evidence-based Clinical Practice Guidelines for other rare and complex Connective Tissue Diseases (Antiphospholipid syndrome, Relapsing Polychondritis, Mixed Connective Tissue Disease, Ehlers-Danlos Syndromes, Undifferentiated connective tissue disease, IgG4 Related Diseases). This might be explained by the absence of sufficient evidence data to support the development of these recommendations and highlights the need of future studies, which could be supported by the ERN ReCONNET in collaboration with specific study groups and scientific societies (already established for some Clinical Practice Guidelines).

In addition, the supplement also includes a contribution written by the Health Economic Group of Scuola Superiore Sant'Anna (Pisa) who is actively involved in the network for its considerable expertise in pharmacoeconomics. The paper is aimed at obtaining a state of the art of rare diseases policies and initiatives in the ERN ReCONNET countries, collecting and analysing the rare diseases national plans of all the eight countries of the ERN ReCONNET participants.

Finally, this supplement offers all together, the 'state of the art' on Clinical Practice Guidelines available for complex and rare Connective Tissue Diseases and might serve also as knowledge background for the development of the tools for the analysis of organisational and economic aspects related to the diagnosis and management of rare and complex connective tissue diseases.

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