

REVIEW

Rare diseases under different levels of economic analysis: current activities, challenges and perspectives

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ABSTRACT

Rare diseases imply clinical and economic burden as well as a significant challenge for health systems. One relevant objective of the activities planned within the European Reference Network on Rare and Complex Connective Tissue and Musculoskeletal Diseases (ERN ReCONNET) is to address the economic dimensions of rare diseases to identify, develop and suggest strategies to improve research and patients' access to orphan drugs (ODs) and highly specialised health technologies. This paper presents a preliminary review of the existing policies on rare diseases in the countries of the Network members. It also introduces and discusses the theme of *how to perform health economic evaluations* of rare diseases and of existing or new treatments for rare diseases. To obtain a preliminary overview aiming at defining the state of the art of rare diseases policies and initiatives in ERN ReCONNET countries, we collected and analysed the rare diseases national plans of all the eight countries of the ERN ReCONNET participants. The preliminary overview that has been performed showed that in all the ERN ReCONNET countries are in place national plans for rare diseases; however, heterogeneity exists in the reimbursement of ODs, direct provision by the healthcare system, involvement of patients' associations in decision making and implementation of clinical practice guidelines.

ECONOMIC AND ORGANISATIONAL CHALLENGES OF RARE DISEASES

In Europe about 30 million people (1 in 17) suffer from a debilitating rare disease (in Europe, a disease is considered rare if it affects 1 person per 2000). Rare diseases imply great clinical and economic burden but also a significant challenge for health systems because of the risk of not responding to patients' needs and of not guaranteeing equal access to treatment.¹

To address the challenge of rare diseases, the European Commission has selected as strategic objective the improvement of patient access to diagnosis, information and care, and defined specific measures to increase resource use across the European Union (EU). These

Key messages**What is already known about this subject?**

- ▶ Rare diseases (RDs) imply great clinical and economic burden but also a significant challenge for the overall healthcare system related to the risk of not responding to patients' needs and not guaranteeing equal access to treatments.
- ▶ Despite the efforts made by European and national health organisations to address the economic evaluation issues about RDs, a widely accepted approach for guidelines and practices is still needed.

What does this study add?

- ▶ This paper presents a preliminary review of the existing policies on RDs in the countries of the European Reference Network on Rare and Complex Connective Tissue and Musculoskeletal Diseases (ERN ReCONNET) members.
- ▶ The study also introduces and discusses the theme of how to perform health economic evaluations in RDs.

How might this impact on clinical practice?

- ▶ Supporting the diffusion of novel approaches to perform valuable economic evaluations of RD issues could contribute to the fast and rapid diffusion of best clinical practices and treatments in Europe.

include, in particular, improving recognition and visibility of rare diseases, standardising the coding of rare diseases in all health information systems, supporting national plans for rare diseases, and promoting and funding the creation of European Reference Networks (ERNs).

Among the challenges EU is asking to cope with, we focus on the economic perspective for rare diseases.

In particular, the following are the most relevant dimensions related to the health economic evaluation of existing and new solutions for treating rare diseases:

1. The research-related clinical issues regarding the understanding of the disease and



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the diagnosis (ie, lack of familiarity with the rare disease, disease heterogeneity, lack of established diagnostic criteria, misdiagnosis, geographical variation), the development of effective treatments (ie, heterogeneity of treatment effects) and the recruitment of patients (ie, geographical limitations, disease coding systems, ethical and privacy issues).

2. The demonstration of the value for money, the achievement of reimbursement and patients' access to care (lack of sufficient clinical data, lack of validated instruments to assess relevant endpoints).
3. The equity of access and other social concerns (economic pressure on healthcare budgets, unmet needs, equal access to high-quality healthcare services and to technology across geographical regions).²
4. The techniques and tools to be used for performing the health economic evaluation of alternative care/therapeutic approaches for rare diseases.

In this scenario, only a multilevel, multidimensional strategy can be effective for managing such a complex problem.

THE EUROPEAN RESPONSE

The European response to economic and organisational challenges

Since the end of the 20th century, the issues and implications of rare diseases and orphan drugs (OD) policy were under the concerns of the European institutions.³ More precisely, starting in 1999 with the (EC) 141/2000 on Orphan Medicinal Products,⁴ the European Community began a series of legislative and policy commitments around strategies to improve public health and care plan for rare diseases.

This regulation act established for the first time in Europe the standard definition of rare disease, setting in not more than 5 per 10 000 persons affected the maximum value of the prevalence that defines a disease as a rare one. As well, the EU regulation n. 141/2000 underlined the need at the national level to offer more incentives in favouring the recognition and treatment of rare diseases, and in incentivising drug development, whose research and development costs may not be covered only by market sales.

In 2008 the European Commission realised a report,⁵ underlying the necessity to put more efforts in tackling rare diseases as a public health policy issue that requires a set of application strategies and guidelines coherent at the European level to support specific actions in the Member States. As a result, in 2009 the European Council of health ministries adopted an action plan for rare diseases in which a set of detailed recommendations triggered the development and adoption of national plans for rare diseases by the end of 2013.⁶

Meanwhile, many projects were financed by the EU under the framework programme of the community action in the area of public healthcare.⁷

Moreover, rare diseases action programme was heavily addressed in 2011 with the Directive EU n. 24 on the

application of patients' rights in cross-border healthcare.⁸ The goal of the directive was to improve the access and the possibility to share practices and interest about rare diseases care across the European Member States. The directive identified the main circumstance in which patients can seek care in other EU countries than the residential one, and Article 12 provided the development of the ERNs.

The European Directive on the application of patients' rights in cross-border healthcare established in 2011 a legal framework for cross-border healthcare in Europe and favoured cooperation between the health systems also with the promotion of ERNs.^{9–11}

The establishment of ERNs has the aim to create excellent organisational and clinical models around 'families' of rare diseases, grouped on the basis of clinical areas, to allow inclusiveness and overcome fragmentation characterising single rare diseases. The idea is to support and favour the linking of European centres of expertise and professionals in different countries to share knowledge and identify alternative treatment options, and to facilitate research and spread innovation, with the ultimate goal of allowing all EU patients to have access to the best care.¹² Support and cofunding to ERNs were provided by the European Commission.¹¹ After the evaluation of 5-year priorities and objectives, a total of 24 ERNs were launched in March 2017, and among these ERN ReCONNET is the ERN on Rare and Complex Connective Tissue and Musculoskeletal Diseases (rCTDs). The ERN ReCONNET multiannual work plan (5-year plan), taking the challenge of the 'economic dimension' of rCTDs, also includes organisational and economic dimensions as among the priorities to be addressed involving experts in the context of rheumatic disease and their economic impact,^{13–22} and networking with different professionals and patient representatives.

The idea is that in the frame of the collaborative intelligence created within and across the ERNs, to face and discuss the issue of organisational and economic dimensions will be necessary to achieve the overall goal of delivering and providing access to the best possible care.

This objective will be pursued taking into account also matured experience in the field in recent years. Nowadays in EU countries even though there are still difficulties and disparities in the development and reimbursement of ODs (ie, drugs that are able to treat diseases so rare that, under usual market conditions, pharmaceutical companies are reluctant to develop them) and in the provision of innovative and highly specialised health technologies (HSHTs) for the diagnosis and treatment of rare diseases, in the last years some initiatives have been developed to deal with economic and organisational challenges of rare diseases.¹² European research projects such as Social Economic Burden and Health-Related Quality of Life in Patients with Rare Diseases in Europe (BURQoL),²³ European Network for Health Technology Assessment (HTA)²⁴ and Advanced HTA,²⁵ and special interest groups such as the National Institute for Health and Care Excellence²⁶ and International Society for

Pharmacoeconomics and Outcomes Research (ISPOR) Rare Disease Group,²⁷ devoted their attention to the challenges of health economics (HE) for rare diseases and OD reimbursement. Available evidence about the implications for HTA in the context of rare diseases as well as examples of frameworks developed in specific contexts where dedicated pathways for HSHTs and ODs have been established are described in a document from the Kidney Disease Improving Global Outcomes and the London School of Economics.^{28–36}

The core message of these initiatives and scientific reports highlights and in some cases defines models for a more comprehensive assessment of the economic and socioeconomic impact of rare diseases, also stressing the importance of valuing the patient's voice.

These efforts did not evolve until now in the practical development of a paradigm shift across EU, nor in the resolution of disparities among countries. Differences in the implementation of rules (eg, health technology assessment) for allocating healthcare resources in general, and in particular in the eventual definition and adoption of specific processes for rare diseases, characterise the current scenario.^{37–40} Moreover, despite the existence and some degree of homogeneity among recommendations across countries, many practices still differ.³⁷

In addition, since 2015 when the EU set the orphan drug designation which established rules to offer incentives for companies to research and develop medicines for rare diseases that otherwise would not be developed,⁴¹ an impact in terms of increasing development and reimbursement of ODs in the EU has still not been demonstrated.⁴²

Rare diseases policies and initiatives in the ERN ReCONNECT countries

At the national level, in Europe, there is heterogeneity regarding the national policies, national plans and strategies for rare diseases. It is the case of countries involved in the ERN ReCONNECT initiative.

The preliminary overview that has been performed showed that in all the ERN ReCONNECT countries are in place national plans for rare diseases.^{43–48} In six countries either some funding initiatives have been designed for the reimbursement of ODs (Belgium, France, Germany, Italy, Portugal) or direct provision by the healthcare system is in place (The Netherlands). The involvement of patient associations in decision making has been integrated in six countries (Belgium, France, Germany, Italy, Portugal, The Netherlands); clinical practice guidelines for rare diseases have been implemented in five countries (France, Germany, Italy, Portugal, The Netherlands); and in four countries funds for the implementation of the plans have been dedicated (France, Germany, Romania, The Netherlands). Finally, in Italy there is a patient pathway dedicated to rare diseases. In addition, [table 1](#) summarizes the main results obtained in the preliminary overview regarding the rare disease activities in ERN ReCONNECT countries. A more detailed description of the results is available in the online supplementary table S1.^{49–59}

Rare diseases national plans are tools for the implementation of public health strategy in the field of rare diseases at the national level. Since 2009 the value of these national plans has been underlined at the European level by the Council Recommendation on European Action in the Field of Rare Diseases (2009/C 151/02), for the adoption of national plans that follow the guidelines and recommendations elaborated by the EUROPLAN project (cofunded by the EU Commission for the promotion and implementation of national plans or strategies in rare diseases). Within the framework of national health and social systems, the national plans should (1) guide the relevant actions to guarantee access to high-quality care and to effective ODs for patients with rare diseases; (2) integrate measures at the local, regional and national levels for a harmonised approach; and (3) define priority actions with operating objectives and follow-up activities. Rare diseases national plans represent the strategies for the constitution of implementation of national (and regional) rare diseases networks. The national networks cooperate with the ERNs in a collaborative manner to establish a common exchange of knowledge and mobility of expertise.

The current approach in health economic evaluation

The process of evaluating healthcare programmes is usually based on the interrelated hypotheses of (1) resource scarcity; (2) technology (drugs or medical devices) as a given good; (3) constant returns of scale for health resource allocation in order to avoid switching phenomena in which an increasing investment could transform a previously dominated solution into a dominant alternative; (4) individual preferences in condition of risk represented by expected utility, and so: rationality of agents and their expectations and heuristics, as refinements adopted to reduce multiple equilibria agents can compute; (5) short-run horizon; (6) finite in number and fixed over time states of nature; (7) equilibrium; and (8) isomorphism, up to symmetric and non-systemic errors, between properties individually observed and inferred from samples to the general population.

Under these hypotheses there is an optimum criterion for allocating resources: ordering alternatives according to their efficiency, that is, on the basis of cost and effectiveness ratios. In the set of endpoints that are usually adopted for measuring the effectiveness of alternative solutions—and despite the increasing objections—utility and expected utility as measures representing patients' preferences in a 'certain'^{60–62} or in a 'risky' world, respectively, are now a standard.

Small samples and high heterogeneity among patients and in the evolution of the disease for each patient are the most relevant challenges in assessing the effectiveness and costs of treatments for rare diseases.

Therefore, we believe that traditional approaches could not be appropriate for assessing the cost and effectiveness of rapidly changing conditions and high heterogeneity, as experienced in rare diseases. New solutions and

Table 1 A summary overview of rare disease activities in ERN ReCONNET countries

Country/ Activities	Centers of expertise for rare diseases	Sharing information, patient support	Clinical Practice guidelines and best practice; Registries	Access to healthcare services and orphan drugs	Organization of care
Belgium	Annual national funded NPRD*; three levels of networks for rare diseases.	Main information provided by RaDiOrg* patients' organization.	CPGs* not produced at national levels. The Central Registry for RDs* is in place. Specific diseases registries also available.	About n. 78 ODs* available (end of 2016).	Neonatal screening programs regulated by regional law.
France	NPRDs since 2004. Third plan 2018-2022 approved on July 2018.	Main information developed and provided by Orphanet.	National standard of care for RDs are provided by reference centres.	Essential services and products may be reimbursed, included off-label products.	Neonatal screening programs available.
Germany	RD centres of expertise implemented by the federal structure of the healthcare system (limited list diseases).	Information developed by Orphanet, and a national helpline for patients was setup.	CPGs available for some rare diseases.	ODs fully reimbursed.	Neonatal screening programs available.
Italy	NPRD 2013-2016 approved in October 2014. National and regional designation process for identification of centres of expertise for RDs (hospitals) since 2001.	Information developed and provided by Orphanet and a national helpline for patients was setup.	CPGs produced and implemented at national level. Registries: National RD Registry and Regional RD registries projects are funded by NHS*.	ODs are provided by the NHS following the same coverage for all other medicinal products.	Neonatal screening programs available. RD patient pathway available.
Portugal	RDs centres of expertise are recognized by an official act of the Minister of Health under a National strategy for RDs.	Information developed by Orphanet, and a national helpline for patients was setup.	CPGs produced and implemented at national level. Nonnational or regional registries.	Patient access services provided by RD card since 2013. NHS covers all patients on a national reimbursement list basis.	Neonatal screening programs available.
Romania	NPRD adopted at the end of 2013 funded through national legislation (no dedicated budget).	Public funded national RDs information, helplines are in place.	No CPGs for RDs. (at the date of 2016). National or regional RD registries missing. Disease specific registries available.	Some genetic tests are provided to patients free of charge. ODs are both commercialized and free of charge for patients.	Not found
Slovenia	NPRD adopted covering the period 2012-2020.	Information developed by Orphanet, and a national helpline for patients was setup.	CPGs adopted at national level for some diseases.	Specific programs and facilities are in place to support people with RDs (individual care plans, access to social and support services).	Neonatal screening programs available.
The Netherlands	NPRD adopted in 2003 with allocated structured budget.	Information developed by Orphanet, and a national helpline for patients was setup.	NCPGs produced. A national policy for development, adoption and implementation of CPGs is in place.	ODs fully reimbursed.	Neonatal screening programs available.

*NPRD, National Plan for Rare Diseases; RDs, Rare Diseases; RaDiOrg, Rare Disease Organization Belgium; ODs, Orphan Drugs; CPGs, Clinical Practice Guideline and best practice; RDs, Rare Diseases; NHS, National Healthcare System.

methods can transform the current paradigm of analysis as discussed in the following paragraph.

Recommendations for performing economic evaluation in rare diseases

Alternative approaches: complexity, heterogeneity and evolution *Agent-based modelling*

Appearing more suitable for assessing the impact of new therapies in a changing environment, alternative evolutionary-based paradigms, if adopted for a dynamic HTA, can be more appropriate for assessing and comparing rare disease therapies.

Alternative approaches like *agent-based modelling* (ABM) will allow health economists to take into account heterogeneity, adaptation and learning, a mix that is the true endogenous engine of the evolution of social and interacting systems; to reproduce the effects of institutions on individual behaviours and the health and economic global variables; to analyse interactions and emerging patterns in evolving environments; and to inform policy decision makers on the emerging effects of changes. Moreover, by modelling the behaviour of multiple agents (those relevant figures involved in the problem, that is,

patients, caregivers, clinicians, policymakers and so on), ABMs have the potentiality to capture the spectrum of consequences and effects produced by rare diseases, and rCTDs too, that go also beyond the mere clinical picture or effectiveness and involve the specific interaction with available treatment, and the interplay of patients (and their heterogeneity) with peers and with the overall environment they live in (the health systems too).

While the first applications of ABMs in health disciplines found their natural application in simulating the effects of virus contagion from infectious diseases, like HIV and influenza, due to agents' interactions and some vaccination policies^{63–66} due to their flexibility, ABMs have been currently adopted for modelling the interaction of heterogeneous agents and different stakeholders in the treatment and management of some chronic diseases.⁶⁷ The use of this kind of models is also challenging in evaluating possible drivers of treatment efficacy and effectiveness and their clinical and economic impact, as the impact of medication adherence and/or non-adherence in the evolution of rare diseases.⁶⁸

In brief, new approaches will overcome the limits of the current methods (mainly based on *ad hoc*, *time and spatially constrained* experiments), making heterogeneity and complexity experienced in case of rare diseases a source of information rather than an obstacle to be bypassed for a real surveillance over time.

The Big Data perspective

The importance of the environment patients live, their interaction with peers and in particular social interaction also bring to the potential of the Big Data analysis. The emergence of Big Data analysis is nowadays largely recognised as one of the most important socioeconomic shifting paradigms derived from digital socialisation,⁶⁹ supported by social networks and the technological improvement of cloud technology.⁷⁰

The Big Data revolution is able to sustain the shift from the current to a new era of HTA indicated for a dynamic perspective in assessing the impact of therapies adapted for rare diseases.

Some examples on study design and statistical methods are presented and discussed below.

Study design and data collection towards a dynamic approach

The exclusive positioning that randomised clinical trials (RCTs) are occupying in the scale of evidence came to be reconsidered. Novel adaptive-based (AB)^{71–79} and pragmatic approaches appear more challenging. In this, although AB trials are biased (this bias, however, can be controlled), they have the advantage over RCTs on the probability that, on average, patients receive the most effective therapy (adopting a Pólya urn approach, a simple demonstration of this is available in Mahmaud⁸⁰).

This method has some relevant limitations, such as that it needs more time than a traditional one, while the most relevant challenge is that it is able to mime the current clinical practice where physicians adapt and learn on the

basis of the observed reaction to therapies. The current practice should be considered a continuum and ongoing adaptive clinical trial through which we can observe and learn, updating our knowledge on the disease and its evolution (ie, a natural synthesis between adaptive control trials and the Bayesian approach).⁸¹

In this, rare diseases could become the first application of a new dynamic approach on HTA in which there is no more distinction between analyses on trial and continuum analysis on the current practice.

To improve the comparison of studies and obtain more information from analysis and meta-analysis, a fundamental direction for HTA in rare diseases is the creation of an EU standard that encourages researchers and scientists to adopt the same criterion for selecting the more appropriate methodologies for the analysis. Big data and international registries could improve our knowledge on the field, and heterogeneity could be a resource only in case of homogeneous or comparable methods of analysis.

Statistics

A dynamic HTA needs a rethinking of the approaches usually adopted for analysing data. In this scenario, two alternatives are available.

Providing the current traditional framework for the health economic evaluation, the frequentist/classical approach (FA)^{82–83} relies on the assumption that an uncertain phenomenon can be described by an unknown probability distribution whose parameters are fixed and their values could be estimated sampling from that distribution. This approach can experience limits in case of rare diseases.

As opposed to the frequentist approach, the Bayesian perspective (BP)⁸⁴ conceives probability distributions associated with a phenomenon as the model of our knowledge/ignorance for that phenomenon. Our knowledge/ignorance is updated according to the availability of novel evidence and information.

In this, BP is closer to the concept of 'learning by data' and inductive reasoning, and it also better copes with the possibility of continuously updating knowledge.

To also catch the opportunities offered by the widespread diffusion of Big Data, no definite advice probably exists in the dilemma of adopting FA or BP or hybrid approaches⁸⁵; it depends on the specific situation we are in.

Nevertheless, the apparent balance and comparability of FA and BP could not be the same when we are interested in assessing the impact of HTA in the rapidly changing and complex environment of rare diseases.

CONCLUSIONS

In a context where organisational and economic issues about rare diseases are still a challenge and there is high heterogeneity in guidance and practice as well as lack of transparency or methods,⁸⁶ ERN ReCONNET can offer a real opportunity to develop novel solutions to

address current challenges and issues related to rCTDs. At the same time, rCTDs could also be the ideal context for testing potentialities and limits of the novel HTA approaches, as a starting point for applications in other contexts and diseases.

Diffusion of novel approaches, when proven to provide advantage, requires a new mentality among all the professionals and stakeholders involved (eg, decision makers, health economists, clinicians and so on), which could be driven by the development of a 'guide' concerted with relevant stakeholders.

In conclusion, this work represents the first summary of an overall identification of the different economic evaluations for rare diseases in Europe, the state of the art, and a descriptive analysis of how governments and local authorities try to tackle this issue.

Moreover, to the best of our knowledge, currently there is a lack of general guidelines for performing economic evaluations of rare diseases, which implies the necessity to coordinate in developing a wider and more effective comprehension of the best practices and activities able to fill this lack.

As a future task, this work aims at overcoming the limits of this preliminary analysis and updating the knowledge of economic evaluation for rare diseases with more evidence on methods and approaches when these become available in ERN ReCONNET.

Future activities will be focused on defining guidelines for assessing the effectiveness and costs of alternative therapies for rare diseases considering the existing and new paradigms of analysis within the ERN ReCONNET network.

Two related questions are mandatory to cope with rare diseases in the years to come. First, how to fund and incentivise research on and second how to reimburse the research outcomes in rare diseases. The second question indicates a specific issue that needs solutions: which criteria, methods and tools (also far from a traditional measure of efficiency) can be adopted to estimate the economic and social burden of a rare disease, and to compare alternative solutions in a budget constraint scenario. These questions can be resolved only at an international level through new connections and team working of experts coming from different initiatives and international networks for rare diseases.

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