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The view of experts on initiatives to be undertaken to promote equity in the access to orphan drugs and specialised care for rare diseases in Spain: A Delphi consensus

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ABSTRACT

Objectives: To reach a consensus amongst experts on the most feasible actions to be undertaken to facilitate patient access to specialised care and orphan drugs (OD) in the public health sector in Spain.
Methods: Two Delphi rounds were completed. The questionnaire was based on a literature review and 2 focus groups. Agreement was sought on the desire (D) and prognosis (P) for the implementation within the next 5 years, on a 5-point Likert scale. Consensus was reached when ≥75% participants chose agreement (1–2) or disagreement options (4–5).
Results: 82 experts on rare disease (RD) participated. Agreement on the D and P was reached in 66.07% statements: OD pricing review [absence of clinical effectiveness (D:85.37%; P:85.90%), target population increase (D:79.27%; P:91.03%)]; reference team definition of referral protocols and clinical practice guidelines (D: 97.56%; P: 89.74%); and a unified, usable, etiology-based registry (D:97.56%; P:84.62%). D and P assessment diverged in 32.14% items: creation of a specific funding system for OD (D: 97.56%; P: 60.25%); and a network of medical teams to coordinate the care of RD patients (D: 99%; P: 62%).
Conclusions: The results have shown the need to promote dialogue between stakeholders, introduce European recommendation to national and regional Spanish policies and set up priorities and undertake actions to drive relevant changes in current medical practice in managing RD patients.

1. Introduction

Rare diseases are an important public health issue and a challenge for the medical community, not only due to the clinical and therapeutic complexity they represent, but also because of the lack of knowledge regarding their natural course, which jeopardises prompt diagnosis and the anticipation of serious risks with undesirable outcomes [1]. Although rare diseases affect a limited number of persons, defined in the European Union as 1 in 2000 individuals or less [2], according to the World Health Organisation, between 5000 and 8000 disorders are defined as "rare" [3]. It has been estimated that about 3 million individuals may be affected in Spain [4].

The vast majority of rare diseases are often severely disabling, substantially compromise life expectancy, and impair physical and intellectual abilities [5,6], converting the problem into a truly social

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health issue and a major public health concern [7]. Broad differences in the management of patients with rare diseases have been reported between centres and across regions worldwide, particularly in the type and nature of services that are made available to patients [8–10]. Several political efforts have been made by the European member states to help patients and families access prompt and proper care [4,11,12]. However, their usefulness may be limited, since the political, social, scientific and economic context has changed since these policies were implemented, and particularly when country-dependent inequalities in patient access to orphan drugs and specialised care are considerable [13]. Policies affecting orphan drugs and rare diseases, national pricing and reimbursement strategies, and the organisation of healthcare system must be further refined [14].

In Spain, the decentralisation of health services to the country's 17 autonomous communities has led to the emergence of a variety of management models, uneven distribution of the drugs supplied by the system, and varying medical practices [15]. Despite political efforts, these variations result in wide differences in patients' access to care and treatments [16–18]. Although evidence is available on the views of patients and carers [19], little is known about the perception of medical experts and healthcare stakeholders regarding actions that need to be undertaken to realistically guarantee equity in the nationwide access to optimal treatment and care of rare diseases. We selected a Delphi consensus technique to address this issue. The Delphi is a research method aimed at reaching agreement on specific issues and possible solutions in the future [20]. It is a structured process that consists of the application of subsequent questionnaires in a series of rounds in which the responses of the group to one round are used to produce the questionnaire for the next round, providing feedback to respondents in each consecutive round [21]. The study objective was to determine the level of agreement among stakeholders regarding the realistic implementation of a series of initiatives for improving access to care and treatments for rare diseases in a 5-year time horizon in Spain.

2. Methods

A national, online, 2-round Delphi consultation was conducted. The 4 key elements were assured, including systematic testing of experts' opinion over a series of rounds, anonymity of participants to reduce the potential for dominant individuals to influence group opinion, controlled feedback of responses to diminish the effect of group noise, and the statistical aggregation of group responses [22]. Two rounds were considered sufficient to reach consensus, as more rounds would have increased potential response fatigue and withdrawal of participants without additional shift or stability in responses [23]. The following steps (Fig. 1) were followed:

2.1. Study scientific committee

A study scientific committee was designated to oversee the development of the study, comprising 7 rare disease experts from internal medicine, paediatrics, orphan drugs evaluation, rare disease registries, and patients' and pharmaceutical industry representatives. They were chosen on the basis of their longstanding expertise and active involvement in scientific and political initiatives for rare diseases in Spain.

2.2. Literature review and focus groups

An extensive review of the literature was conducted in international database [PubMed, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), National Health Service (UK) Economic Evaluation Database (NHS-EED)], Spanish databases [*Consejo Superior de Investigaciones Científicas Biomedicina* (CSIC-IME), *Medicina en español* (MEDES) and *Índice Bibliográfico Español en Ciencias de la Salud* (IBECS)] and grey literature, to examine existing publications and to identify international and national initiatives that directly and indirectly influenced Spanish policies on rare diseases and orphan drugs, published between 1st January of 2005 and 30th June of 2014. Information provided by the publications reviewed was summarize in 4 mains blocks: 1) orphan drug pricing and reimbursement, 2) Access to orphan drug and health care, 3) Orphan drug status and, 4) Orphan drug and rare disease registry.

Two focus groups (n = 13 participants) made a detailed report of professionals' perceived needs and challenges for managing patients with rare diseases and for accessing orphan drugs in everyday practice in Spain. Focus groups participants included: clinicians, paediatricians, hospital pharmacists, healthcare managers (hospital manager and healthcare policy makers at regional and national level) and patient representatives.

2.3. Contents of the Delphi consultation: first and second questionnaires

Four groups of data were defined and addressed in the first questionnaire (Appendix A): orphan drug pricing and reimbursement (5 issues); access to specialist care and orphan drugs (19 issues); rare disease registries (7 issues); and care models for rare diseases management (1 issue). Two possible models of care for rare disease patients in Spain were defined. Both models shared common features, including the existence of a specific funding system for rare diseases and rare disease reference teams working in coordination with local care teams. The key difference between models was the coordination of healthcare for rare diseases, either centralised or decentralised.

All statements assessed the participants' desire and prognosis (prediction or forecast) that each statement would be realised within a 5-year period, on a 5-point Likert scale (from 1 = *in total disagreement*; to 5 = *in total agreement*). The study scientific committee reviewed the questionnaire to ensure that statements were clear, unambiguous and non-leading. A blank space was included at the end of the first questionnaire for participants to make comments on the issues addressed.

The second questionnaire included all statements for which consensus was not reached in the first round. In the second questionnaire, each Delphi panellist received their own scores together with the summary score given by the group to the same statement in the previous round.

2.4. Delphi panellists

Panellists were nominated by the study scientific committee or identified by the Internal Medicine, Neuropaediatrics and Hospital Pharmacy Scientific Societies. Panellists included clinicians, paediatricians, hospital pharmacists, healthcare managers (hospital manager and healthcare policy makers at regional and national level), representatives from the pharmaceutical industry, and members of patients' associations involved in rare disease management and orphan drugs decision making.

2.5. Sample size

There is little consensus in the literature concerning the optimal sample size of a Delphi study [24]. Taking into account that 10–15 subjects could be sufficient to reach a solid consensus if their background is homogeneous1, a sample size of 75 subjects (15 participants per discipline) was deemed adequate.

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