DIFFERENTIAL ASPECTS OF ORPHAN DRUGS AND THEIR VALUE FROM A SOCIAL PERSPECTIVE

aelmhu

Fundación Weber

DIFFERENTIAL ASPECTS OF ORPHAN DRUGS AND THEIR VALUE FROM A SOCIAL PERSPECTIVE

May 2024

Made by: Fundación Weber

In collaboration with: aelmhu spanish association of orphan and ultra-orphan drug laboratories

Authors

Néboa Zozaya
Director of the Health Affairs & Policy Research department
Weber

Fernando Abdalla
Consultant in the Health Affairs & Policy Research department
Weber

Javier Villaseca
Consultant in the Health Affairs & Policy Research department
Weber

Irene Fernández
Consultant in the Health Affairs & Policy Research department
Weber

Álvaro Hidalgo
President of the Weber Foundation

Edited by

© Fundación Weber
C/ Moreto 17, 5º Dcha.
28014, Madrid

Editorial coordination:
weber@weber.org.es

ISBN: 978-84-126632-6-6

D.L.: M-3750-2024

DOI: https://doi.org/10.37666/I22-2024

Madrid, May 2024

INDEX

LIST OF ACRONYMS

AC	Autonomous communities
ADA-SCID	Adenosine deaminase severe combined immunodeficiency
AELMHU	Asociacién Española de Laboratorios de Medicamentos Huérfanos y Ultrahuerfanos
AEMPS	Spanish Agency for Medicines and Health Products
AI	Artificial intelligence
AIFA	Italian Drug Agency
ALS	Amyotrophic Lateral Sclerosis
AML	Acute myeloid leukaemia
ATU	Temporary Authorisation for Use
BIG-IV	Botulism Intravenous Immune Globulin for Human Botulism
BR	Background regimen
CAR-T	Chimeric antigen receptor cell therapy
CF	Cystic fibrosis
CFTR	Fibrosis transmembrane conductance receptor
CH	Congenital hypothyroidism
CHMP	Committee for Medicinal Products for Human Use
CIBERER	Centro de Investigación Biomédica en Red (Biomedical Research Network Centre)
CLN2	Neuronal ceroid lipofuscinosis type 2
CML	Chronic myeloid leukaemia
COMP	Committee for Orphan Medicinal Products and Orphan Drugs
CSUR	Reference centres, services or units
CT	Clinical Trial
DLBCL	Diffuse large B-cell lymphoma
EMA	European Medicines Agency
EPP	Erythropoietic photoporphyria
ERDRI	European Rare Disease Registry Infrastructure
ERN	European Reference Networks
EU	European Union
EUPATI	European Patients' Academy
EURORDIS	European Association of Rare Diseases
FDA	Food and Drug Administration
FEDER	Spanish Federation for Rare Diseases
FEV	Forced expiratory volume
FIH	First in Humans
GA-I	Glutaric acidemia type I
G-BA	(Gemeinsame Bundesausschuss) Federal Joint Committee
GO	Gemtuzumab ozogamicin
HAE	Hereditary angioedema
HAS	Haute Autorité de la Santé
HI	Horizontal Health Inequity Index
HIV	Human immunodeficiency virus
HCY	Homocystinuria
IBR	Inference based on randomization
ICER	Incremental cost-effectiveness ratio
IIER	Institute for Research on Rare Diseases
IMPC	International Mouse Phenotyping Consortium
IPF	Idiopathic pulmonary fibrosis
IRDiRC	International Rare Diseases Research Consortium
IVA	sovaleric acidemia
JCA	Joint Clinical Assessment
LCHADD	Long-chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency
LGBQT+	Lesbian, Gay, Bisexual, Transgender, Queer and Other Sexual Orientation
MA	Marketing Authorization
MCADD	Medium-chain acyl-coenzyme A dehydrogenase deficiency
MDR-TB	Multidrug-resistant tuberculosis
MLD	Metachromatic leukodystrophy
mRNA	Messenger ribonucleic acid
MSUD	Maple syrup urine disease
NC	National Code
NICE	National Institute for Health and Care Excellence
NHS	National health system
NMO	Neuromyelitis Optica
NSP	Newborn Screening Programme
OECD	Organisation for Economic Co-operation and Development
ODD	Orphan Drug Designation
OMPs	Orphan Medicinal Products
PERTE	Strategic Projects for Economic Recovery and Transformation
PKAN	Pantothenate Kinase-Associated Neurodegeneration Disease
PKU	Phenylketonuria
PNH	Paroxysmal Nocturnal Hemoglobinuria
PREM	Patient-reported experiences
PROM	Patient-reported outcomes
QALY	Quality Adjusted Life Years
R&D	Research and Development
REeC	Spanish Registry of Clinical Studies
ReeR	Registro Estatal de Enfermedades Raras (Spanish Rare Diseases Register)
RDs	Rare Diseases
SCD	Sickle cell disease
SCID	Severe combined immunodeficiency
SMA	Spinal Muscular Atrophy
SMC	Scottish Medicines Consortium
SMEs	Small and medium-sized enterprises
SOS	Sinusoidal obstructive syndrome
SpainRDR	Spanish Network of Rare Disease Registries for Research
TPR	Therapeutic Positioning Report
UMN	Unmet medical need
US	United states
UK	United Kingdom
VOD	Veno-occlusive disease

Introduction

Context

Rare diseases (RDs), also known as orphan or minority diseases, are pathologies, mostly of genetic origin, that arise in childhood. They are complex, chronic, heterogeneous and scientifically challenging diseases that, despite their diversity, are in many cases degenerative and life-threatening.

RDs are conditions that often present significant challenges for diagnosis, treatment and research due to a lack of medical information and expertise. They are characterised by a low incidence, affecting only a small percentage of the population. In Europe, a rare disease is defined as a disease that affects less than 1 in 2,000 people.

It is estimated that there are more than 7,000 different rare diseases in the world[1], of which almost 6,200 have been identified. Although RDs are not common, the total number of people affected by these conditions is significant. It is estimated that, overall, between 3.5% and 8% of the world's population could be affected by a rare disease at some point in their lives[2,3] (around 300 million people in total). In Spain, about 3 million people are affected by rare diseases[1].

RDs represent a significant economic burden on health systems and society. They often entail a significant social burden due to the high cost they represent in terms of personal care needs, reduced work productivity, the need for complementary therapies and their impact on the quality of life of patients and their relatives[4,5]. In Spain, it is estimated that the average direct health care costs of RDs as a whole are 16,513 euros, as well as 15,557 euros in terms of informal health care direct costs and 4,579 euros in formal health care[6] . In the United States, the economic burden of 379 RDs has been estimated at $997 billion, with 45% being direct healthcare costs, 44% productivity losses, 7% non-health costs and 4% costs not covered by health insurance[7].

Therefore, this group of diseases represents a significant economic burden, and the availability of specific treatments plays a crucial role in reducing it. In fact, it has been estimated that lack of treatment leads to a 21.2% increase in total costs per patient per year[8]. However, 95% of RDs have no specific treatment.

Orphan medicinal products (OMPs) are medicines that are intended to treat rare diseases. The European Commission defines orphan medicinal products as follows[9]:

1. Product intended for a condition whose prevalence does not exceed 5 cases per 10,000 inhabitants in the European Union (EU).
2. A life-threatening, serious and chronic condition.
3. Disease for which there is no satisfactory method of diagnosis, prevention or treatment authorised in the EU. If such a method exists, then the medicinal product must demonstrate that it provides a significant benefit compared to the already authorised product.

Current problems

OMPs face several challenges in terms of research, access and regulatory process. On the one hand, the process from discovery and development of a new molecule to its commercialisation is long (10 years on average), risky (only 1 in 10 molecules tested usually has a therapeutic effect) and costly (several tens of millions of euros), making it generally difficult to recover the capital invested in research with the (few) sales produced. For this reason, OMPs are not always attractive to sponsors and therefore require institutional support.

In addition, OMPs face greater challenges than other drugs in terms of research, with clinical trials (CT) that are necessarily small in size, making planning and execution difficult. As a result, efforts are being made to make the design of clinical trials for these drugs more adaptive and rational.

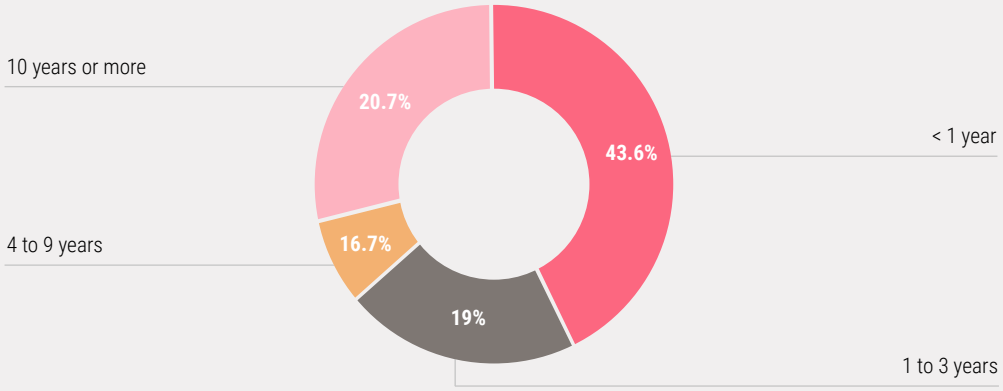
On the other hand, although RDs patients have the same rights to healthcare as any other patient, in practice there are problems of equity and regional access to treatment, due to, among other factors, the complexity of their diagnosis, the lack of medical knowledge and the high cost of treatment.

The problem of diagnostic delay

The diagnosis of RDs remains complex, despite advances in our understanding of these diseases, technological advances and increased resources. The delay in diagnosis is due to a multitude of factors, including the presence of non-specific symptoms, lack of knowledge about thousands of RDs, the point in time at which the patient decides to seek medical help and the availability of diagnostic tests.

According to recent data from the Instituto de Salud Carlos III, obtained from 3,349 patients with RDs from all over Spain, the average time to diagnosis in 2021 was 6.2 years. Of the sample, 56.4% suffered a delay in diagnosis (more than 1 year): 19.0% between 1 and 3 years; 16.7% between 4 and 9 years; and 20.7% 10 years or more (Figure 1)[10].

Figure 1. Distribution of patients with RDs in Spain, by time of diagnosis



Source: *Benito-Lozano (2022)*[10]

Delays of more than 70% were observed in patients affected by diseases classified as mental and behavioural disorders, such as Usher syndrome, Sjügren's syndrome, Behçet's disease, hereditary spastic paraplegia and post-polio syndrome. In contrast, there is a lower risk of diagnostic delay in cancers, haematological diseases, haematopoietic organs and other disorders affecting the immune mechanism as well as congenital malformations, deformities and chromosomal abnormalities.

However, it is worth noting the improvement in diagnostic that have been achieved in recent decades. It is estimated that the time to diagnosis has been reduced at an annual rate of 5.1% between 1974 and 2021[10].

Factors that increase the risk of delayed diagnosis (>1 year from first diagnosis) of a rare disease in Spain include the following[11]:

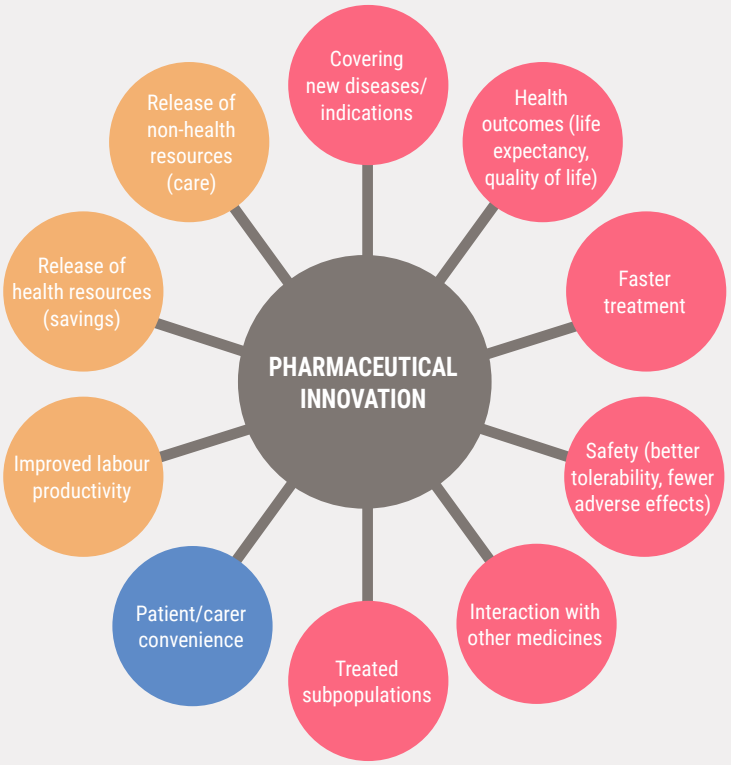
- Go in the first instance to non-specialized medical consultations
- Travel in search of a diagnosis, either to other hospitals or to other Autonomous Communities (AC)
- Number of specialists visited, especially in cases where patients consulted specialists more than 10 times.
- Number of tests performed
- Undergoing surgery related to the rare disease, before a definitive diagnosis is made
- The need for diagnostic genetic testing

Progress and opportunities

In Spain, expenditure on OMPs has followed an upward trend and now represents more than 10% of hospital expenditure on medicines[12]. Some scientific societies are advocating a change of perspective from viewing these costs as expenditure on medicines to considering them as an investment in medicines. This approach implies the imperative need to understand the social value generated by this investment.

The societal value of OMPs refers to the comprehensive contribution that these medicines make to society in addressing RDs. This valuation goes beyond traditional metrics focused on cost and financial benefit, considering the uniqueness of the conditions these medicines treat (Figure 2)[4].

Figure 2. Potential attributes of pharmaceutical innovations in terms of social value



Source: *Mestre-Ferrandiz (2012)*[13]

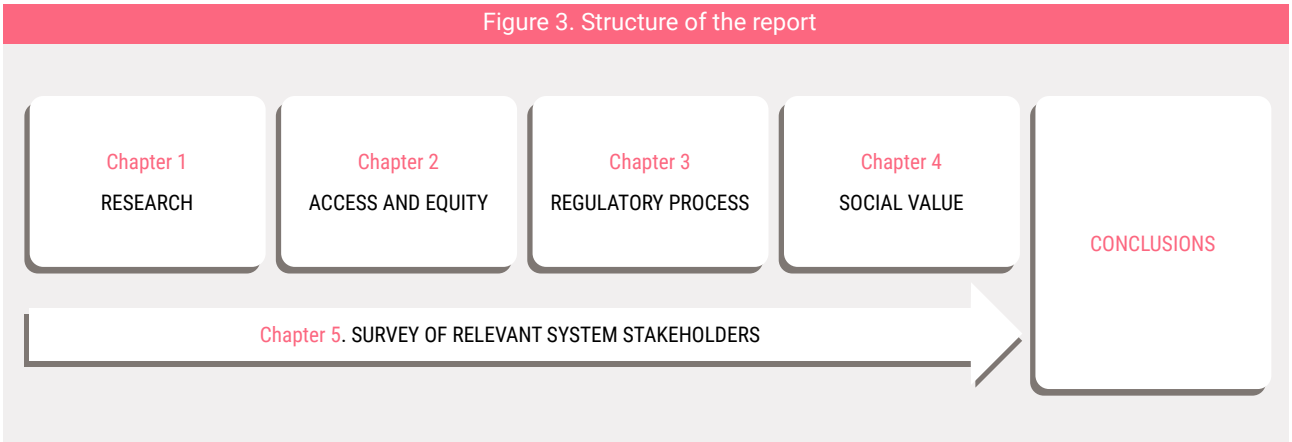
Despite the challenges faced by OMPs, it is important to highlight the significant progress that has been made in the approach to RDs in recent years. Indeed, drugs and advanced therapies have been approved to treat rare diseases with no therapeutic alternatives, such as amyotrophic lateral sclerosis, pulmonary arterial hypertension, hereditary angioedema, Fabry disease, acromegaly, Gaucher disease, cystic fibrosis, hereditary retinal dystrophy, spinal muscular atrophy and haemophilia B, among many others.

Objective and structure of the report

The aim of this report is to compile in a single document relevant and updated information on OMPs, providing published evidence on their differential elements and their contribution of value from a clinical, health and social point of view. In addition, we complement this compilation of evidence with an analysis of the vision of relevant stakeholders of the Spanish healthcare system on the differential aspects of the OMPs and their contribution to social value.

In the first three central evidence-gathering chapters, we address and analyse the elements which differentiate OMPs from other medicines in terms of research, access, regulatory process, evaluation and financing. In addition, in a fourth chapter we provide contrasting scientific examples of the value of OMPs, both in terms of health outcomes and quality of life for patients as well as in terms of efficiency for the healthcare system and society, by avoiding healthcare costs for the system and productivity losses for patients and their families. The fifth chapter summarises the analysis of the survey of some thirty relevant stakeholders. Finally, the conclusions synthesise some final reflections (Figure 3).

Figure 3. Structure of the report



Methodology

To begin with, the central chapters of this report are based on a review of the literature, using Pubmed and Google Scholar as the main search engines. The review focused on finding scientific evidence that showed contrasted and illustrative examples of the contribution of value, as well as compilations of regulations and recommendations from other groups that analysed the current situation and outlining the challenges. The extensive information gathered has been condensed in a consistent and detailed, albeit summarised, manner, with figures to visually illustrate the relevant points.

On the other hand, in order to gather the opinion of the main actors in the system, the Weber Foundation and AELMHU jointly elaborated a questionnaire, based on the information gathered in the chapters, which brought together a total of 20 questions to diagnose the current situation around four distinct themes: the challenges of the OMPs in the field of research, access and the process of authorisation, evaluation and funding; the progress achieved; possible measures to improve the situation; and the social value of the OMPs.

The multidisciplinary panel of experts with knowledge or experience in RDs or OMPs included representatives of the central and regional administration, scientific societies, health technology assessment agencies, patients' associations and other profiles, such as specialists in health economics or health law. The survey was initially sent by email to 70 stakeholders, with Weber sending up to three reminders, resulting in a final sample of 30 responses.

Bibliographic references

1. Spanish Federation for Rare Diseases (FEDER). Learn more about Rare Diseases. [accessed 23 January 2024]. Available at nible at: https://www.enfermedades-raras.org/enfermedades-raras/conoce-mas-sobre-er..
2. Alonso V, Villaverde-Hueso A, Hens M, Morales-Piga A, Abaitua I, Posada de la Paz M. Public health research on rare diseases. Georgian Med News. 2011;(193):11-6.
3. Wakap S, Lambert DM, Olry A, Rodwell C, Gueydan C, Lanneau V, et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum Genet EJHG. 2020;28(2):165-73, doi: 10.1038/s41431-019-0508-0.
4. Farmaindustria. Proposals for Improving Patient Access to Orphan Medicines. 2023.
5. Zozaya, N, Villoro, R, Hidalgo, A, Sanz A, RADEEV Expert Group. Gu'a Metodológica de Evaluación Económica aplicada a Medicamentos Huérfanos. Max Weber Institute. Madrid; 2015.
6. Sequeira AR, Mentzakis E, Archangelidi O, Paolucci F. The economic and health impact of rare diseases: A meta-analysis. Health Policy Technol. 2021;10(1):32-44, doi: 10.1016/j.hlpt.2021.02.002.
7. Yang G, Cintina I, Pariser A, Oehrlein E, Sullivan J, Kennedy A. The national economic burden of rare disease in the United States in 2019. Orphanet J Rare Dis. 2022;17(1):163, doi: 10.1186/s13023-022-02299-5.
8. Andreu P, Karam J, Child C, Chiesi G, Cioffi G. The Burden of Rare Diseases: An Economic Evaluation. 2022.
9. European Parliament and the Council of the European Union. Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. Off J Eur Communities. 1999;2000(18):1-5.
10. Benito-Lozano J, L—pez-Villalba B, Arias-Merino G, Posada de la Paz M, Alonso-Ferreira V. Diagnostic delay in rare diseases: data from the Spanish rare diseases patient registry. Orphanet J Rare Dis. 2022;17(1):418, doi: 10.1186/s13023-022-02530-3.
11. Benito-Lozano J, Arias-Merino G, Gómez-Martínez M, Ancochea-Díaz A, Aparicio-Garc'a A, Posada de la Paz M, et al. Diagnostic Process in Rare Diseases: Determinants Associated with Diagnostic Delay. Int J Environ Res Public Health. 2022;19(11):6456, doi: 10.3390/ijerph19116456.
12. Diariofarma. Medicamentos huérfanos, evaluación y financiación, claves del II post Ispor. diariofarma. [accessed 23 January 2024]. Available at: https://diariofarma.com/2019/03/27/medicamentos-huerfanos-evaluacion-y-financiacion-claves-del-ii-post-ispor.
13. Mestre-Ferrandiz J, Mordoh A, Sussex J. The many faces of innovation. Association of the British Pharmaceutical Industry (ABPI); 2012.

Chapter 1

Research on orphan drugs: distinguishing features

The main challenge in optimising the approach to RDs is to understand the underlying mechanisms of the more than 6,200 RDs identified to date, with at least 4,400 genes associated with these pathologies[1] and ensuring that research and innovation is effectively translated into new diagnostic tools and treatments with proven efficacy.

This challenge is linked to several specificities of OMPs, which will be analysed in this chapter. First, general figures on OMPs in Spain will be provided. Secondly, the complexity of the research and development (R&D) process in OMPs will be highlighted. Thirdly, the distinctive aspects of RDs research will be presented, followed by the exposition of some strategies to address these challenges, through the exploration of alternatives in clinical trial design and outcome variables. Fifth, some additional considerations related to RDs will be described, such as regulatory and financial incentives, recent scientific advances or other aspects.

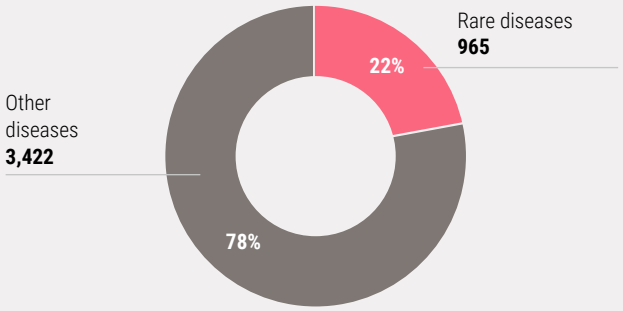
1.1. Research figures about OMPs

In the 21st century, around 35,000 clinical trials have been conducted for RDs globally, evaluating more than 20,000 different pharmacological agents. This high rate of innovation means that 4 clinical trials are initiated daily and 2 innovative pharmacological compounds are explored[2].

In Spain, according to the Spanish Registry of Clinical Studies (REec), 4,387 clinical trials are currently under development (until August 2023). Of this total, 965 trials (22%) focus on RDs (Figure 1). In total, 21,285 people have participated in these trials, resulting in an average of 22 participants per clinical study conducted[3].

Of the 965 trials dedicated to RDs, 90% (n = 869) have been conducted by commercial sponsors. The effective start date was recorded in 84% (n=813) of them from which 82% (n=663) were initiated in the last 5 years (2019- 2023). On the other hand 8% (n = 76) are in phase I, 38% (n = 367) in phase II, 52% (n = 499) in phase III and 2% (n = 22) in phase IV, as shown in Figure 2[3].

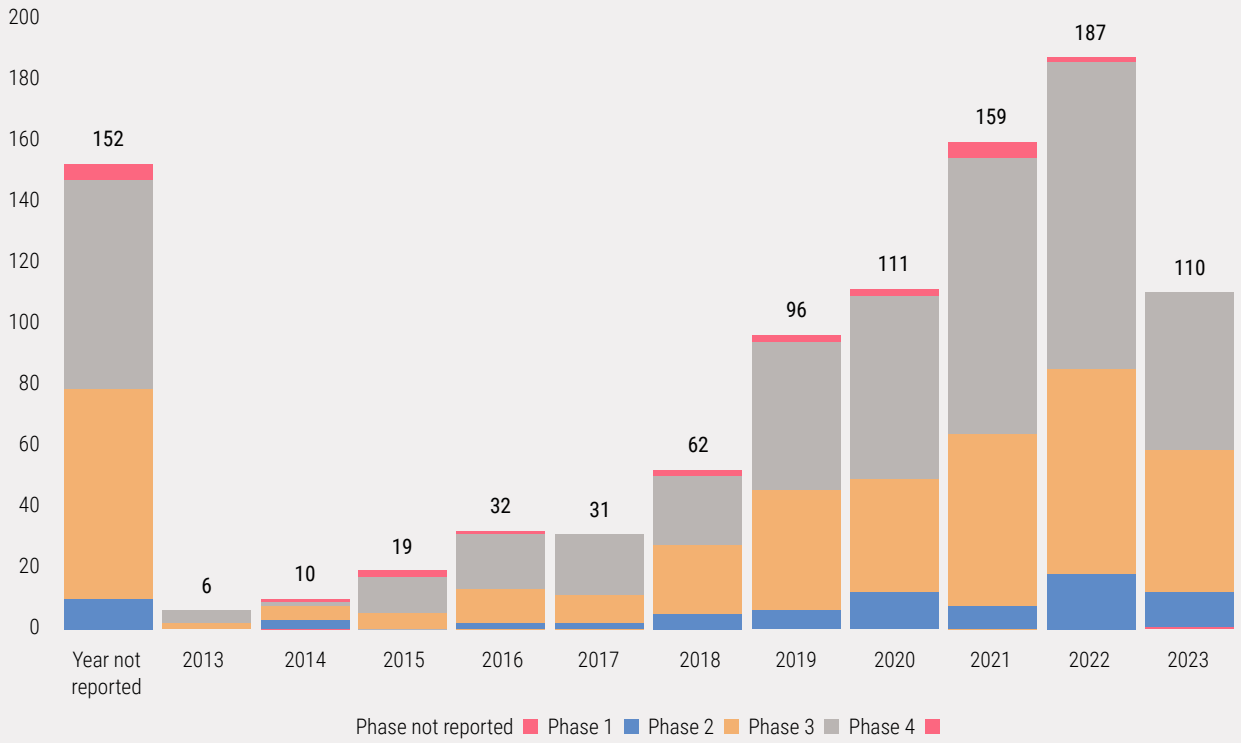
Figure 1. Ongoing clinical trials in Spain, in RDs and other diseases (n = 4,387)



Note: *data until August 2023*

Source: *prepared by the authors based on the Spanish Clinical Trials Register (REec)*[3]

Figure 2. Ongoing clinical trials in Spain on RDs, by start date and phase (n = 965)



Note: *data until August 2023.*

Source: *prepared by the authors based on the Spanish Clinical Trials Register (REec)*[3]

In Spain, seven specific therapeutic areas account for 80% of RD trials under development (n=775). Cancer leads these areas, with 369 trials, equivalent to 38% of the total. It is followed by haematology with 105 trials (11%), immune system pathologies with 86 (9%), the nervous system with 79 (8%), congenital, hereditary and neonatal abnormalities with 73 (8%), musculoskeletal diseases with 35 (4%) and respiratory tract related diseases with 28 trials (3%). Among the 965 clinical studies in development, 51 (5%) are exploring the physiological processes not directly related to diseases, as detailed in Table 1[3].

Table 1. Therapeutic areas of ongoing clinical studies in RDs (n = 965)

Therapeutic area	n	%
Cancer / Neoplasms	369	38%
Haematology	105	11%
Pathologies of the immune system	86	9%
Nervous system	79	8%
Congenital, hereditary and neonatal abnormalities	73	8%
Musculoskeletal diseases	35	4%
Respiratory tract	28	3%
Cardiovascular pathologies	24	2%
Digestive pathologies	22	2%
Physiological processes - Genetic phenomena	19	2%
Physiological processes - Other	18	2%
Ocular pathologies	17	2%
Nutrition and metabolic disorders	16	2%
Physiological processes - Immune system	14	1%
Hormonology	13	1%
Skin and connective tissues	9	1%
Viral diseases	7	1%
Pathological conditions, signs and symptoms	6	1%
Bacterial infections and mycoses	6	1%
Female urology, gynaecology and pregnancy complications	4	0%
Therapeutic, analytical and diagnostic equipment and techniques	2	0%
Multiple therapeutic areas	7	1%
Not specified	6	1%
Total	965	100%

Note: *data until August 2023.*

Source: *prepared by the authors based on the Spanish Clinical Trials Register (REec)*[3]

Of the 965 trials in development for RDs, 67% (651 trials) are exclusively dedicated to the analysis in the adult population (18 years and older), while 21% (199 trials) involve both younger and older patients. The remaining group of trials (115 trials, equivalent to 12%) focus exclusively on the paediatric population. In summary, 33% of RD studies involve the under-18 population, compared to only 11% of studies on common diseases, as shown in Table 2[3].

Table 2. Age ranges in clinical studies (n = 4,387)

Age range	RDs	%	Prevalent	%
Children under 18 years of age	115	12%	188	5%
Mixed: under and over 18 years of age	199	21%	184	5%
18 years and over	651	67%	3,050	89%
Total	965	100%	3,422	100%

Note: *data until August 2023.*

Source: *prepared by the authors based on the Spanish Clinical Trials Register (REec)*[3]

A total of 332 research centres participated in the 965 RDs trials registered in Spain. Almost half (44%) of these centres are located in the region of Catalonia (90; 27%) or in the Community of Madrid (57; 17%). They are followed, in terms of number of centres, by Andalusia (45; 14%) and the Valencian Community (27; 8%). 12 ACs host the remaining 34% of centres (112 centres) (Table 3)[3]

The four hospitals with the largest number of clinical trials (with more than 200 trials) were the Hospital Universitari Vall D'Hebron in Barcelona (418 trials), followed by the Hospital Universitario y Politécnico La Fe in Valencia (266 trials), the Hospital Universitario 12 de Octubre in Madrid (259 trials) and the Hospital Clínic in Barcelona (243 trials)[3].

Table 3. Research sites of ongoing RDs trials, by location (n=332)

Autonomous Community	n centres	%
Catalonia	90	27%
Madrid	57	17%
Andalusia	45	14%
Valencian Community	27	8%
Galicia	22	7%
Castilla y León	16	5%
Basque Country	15	5%
Castilla-La Mancha	11	3%
Canary Islands	10	3%
Extremadura	8	2%
Asturias	7	2%
Aragon	5	2%
Murcia	5	2%
Navarre	5	2%
Balearic Islands	4	1%
Cantabria	4	1%
Not reported	1	0%
Total	332	100%

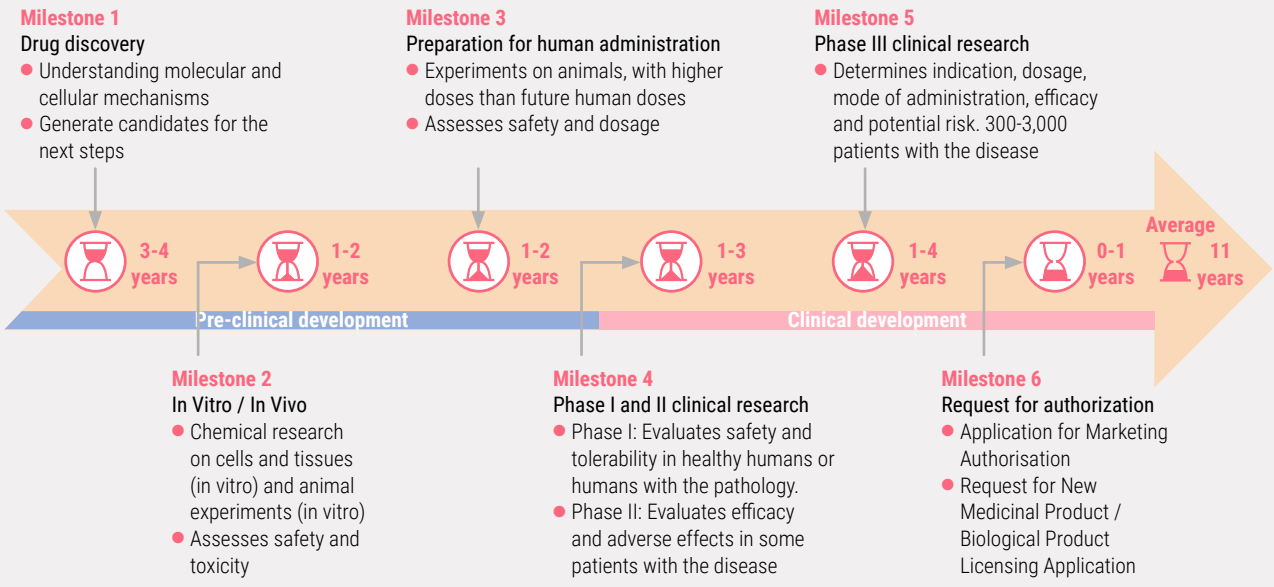
Note: *data until August 2023.*

Source: *prepared by the authors based on the Spanish Clinical Trials Register REec)*[3]

1.2. The process of developing an OMP

The process of developing a new medicinal product[I] for a rare disease is similar to that for prevalent diseases, and generally lasts 10-12 years[4,5]. This process is composed of several milestones, ranging from drug discovery, in vitro and in vivo research, preparation for first-in-human testing, clinical development (phase I to III) and finally, the application for authorisation of the new medicinal product or biological licence[II] (Figure 3)[6].

Figure 3. Milestones in the development of an OD



Source: *own elaboration based on International Rare Diseases Research Consortium (IRDiRC) (2020)*[6]

I *In contrast to the standard development process, the reuse of medicines does not set a specific point for the first phase of human testing.*

II *In this chapter, we will not discuss Phase IV, as this stage begins after a medicine has been approved for use in the general population following Phase I, II and III trials. In this phase, the aim is to assess the drug's performance in real-life scenarios, to analyse the long-term risks and benefits of its use, and to detect possible rare side-effects. The discussion of phase IV will be addressed in subsequent chapters.*

Each key milestones are described in detail below.

Milestone 1: Drug Discovery

The drivers of drug discovery range from the emergence of new insights into the pathological processes, to the evaluation of molecular compounds for therapeutic properties and the occasional discovery of unexpected effects on existing treatments, among others[6].

The process begins with research into the understanding of molecular and cellular mechanisms and their impact on the disease. This phase is known as drug discovery and generally spans a period of 3-4 years. The aim is to generate candidates with suitable pharmacological properties to progress to later stages of development[6,7].

Milestone 2: In vitro and in vivo research

At this stage, two types of pre-clinical research are carried out. Firstly in vitro research, which involves chemical tests on isolated cells, tissues or organs. Then, in vivo research, which is carried out on animals[6]. Validation is achieved when sufficient evidence of biological activity is demonstrated both in vitro and in vivo. In addition, an adequate understanding of pharmacokinetics and pharmacodynamics of the medicinal product is acquired, and preliminary information on its toxicology and safety is generated[6]. This phase may extend over a period of 1-2 years. Based on these data, researchers can plan the next phase.

Milestone 3: Preparation for first human administration

In order to enable the initiation of human testing of pharmaceuticals, regulatory authorities require researchers to evaluate the safety of the product in animals, using doses higher than the corresponding future human doses. These experiments are conducted under highly controlled conditions and are crucial to provide detailed information about dosage and toxicity levels[6]. This phase may extend over a period of 1-2 years[8]. After preclinical testing is completed, researchers carefully review their findings to determine whether the drug in question can be tested in humans[6].

Milestone 4: Clinical research - phases I and II

While pre-clinical research answers basic questions about the safety of a medicine, the research or clinical development phase focuses on how the medicine interacts with the human body[6].

Phase I

A "First-in-Human"(FIH) is the first clinical trial in which the medicine previously tested in animals is tested for the first time in normal volunteers (healthy people). In most cases, 20-80 healthy volunteers or people with the disease/condition participate in this first study (or set of studies), with the aim of providing initial safety and tolerability information, as researchers adjust dosing schedules based on animal data to find out how much of the drug the body can tolerate and what its acute side effects are[6].

However, if a new drug is intended for use in cancer patients or if the administration of the drug poses risks to healthy volunteers (e.g. most of the biotech products), researchers conduct Phase I studies in patients with that type of cancer/RDs mainly for ethical reasons, as there is an urgent need for treatment in serious diseases and conducting Phase I studies in patients can speed up the drug development process by directly involving the target population[6,9].

Purpose: Safety and dosage.

Participants: 20 to 80 healthy volunteers or people with the disease/condition.

Duration of the study: Several months..

Phase II

In Phase II studies, researchers administer the medicine to a (small) group of patients with the disease or condition for which the medicine is being developed. The aim of Phase II studies is to provide the first evidence of biological activity, efficacy and safety in the intended patient population, as well as to select the best dose(s) for subsequent Phase III studies[6].

These studies usually involve several hundred patients and are not large enough to formally demonstrate whether the medicine will accurately predict the safety of the product. In RDs, phase II (or combined phase I-II) studies can be much smaller, sometimes involving only a few dozen patients or even fewer. Their duration is up to 2 years[6].

Purpose: Efficacy and side effects.

Participants: Up to several hundred people with the disease/condition (in RDs sometimes only a few dozen).

Duration of the study: From several months to 2 years.

Milestone 5: Clinical research - phase III

Researchers design phase III studies to demonstrate whether a product offers a treatment benefit to a specific population, i.e. whether or not the benefit-risk ratio of the medicine is positive. Sometimes known as pivotal studies, these trials can involve hundreds or thousands of participants for large therapeutic indications and tens or hundreds for RDs. The data collected in Phase III studies determine the therapeutic indication, dosage and mode of administration, as well as the expected efficacy and potential risk as reported in the patient information leaflet. Because these studies are larger and of longer duration, the results are more likely to show long-term or rare side effects.

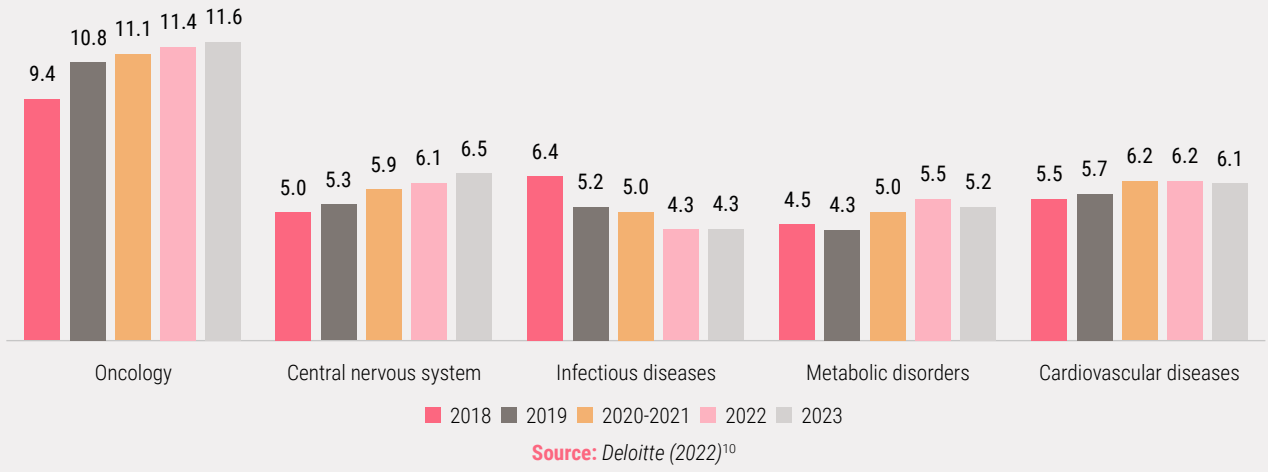
Purpose: Efficacy and adverse event monitoring

Participants:: 300 to 3,000 volunteers who have the disease or condition (tens or hundreds in RDs).

Duration of the study: 1 to 4 years.

Despite the paucity of data on specific development timelines for OMPs, there is evidence that several therapeutic areas have been able to maintain and even reduce clinical trial cycle times over the past 5 years. However, the increase in the length of these intervals was much more pronounced in the field of oncology than in other therapeutic disciplines, reaching an increase of 11.6 years in 2022. This longer time expansion is linked to a number of complex factors, including the increased complexity inherent in the trials and the inherent challenges due to patient selection and retention process[10]. These elements will be examined in greater depth in subsequent sections of this chapter (Figure 4).

Figure 4. Clinical trial cycle times (phases I-III), by therapeutic area



Source: *Deloitte (2022)*[10]

Milestone 6: New Drug Application or Biological Licence Application

If an OMP developer has evidence from pre-clinical and clinical research (Phase I-III) that a medicine is safe and effective for its intended use, the applicant can submit an application to market the medicine to the relevant Regulatory Authority (i.e., the US Food and Drug Administration [FDA], the European Medicines Agency [EMA], etc.). The application for approvals (not the approval itself) usually takes less than a year.

1.3. Distinctive research aspects on OMPs

OMPs research has a number of unique features compared to research on drugs for prevalent diseases. These characteristics often represent obstacles from the conception of a drug to its commercialisation. The most important elements include the following:

➜ Recruitment of clinical trial participants

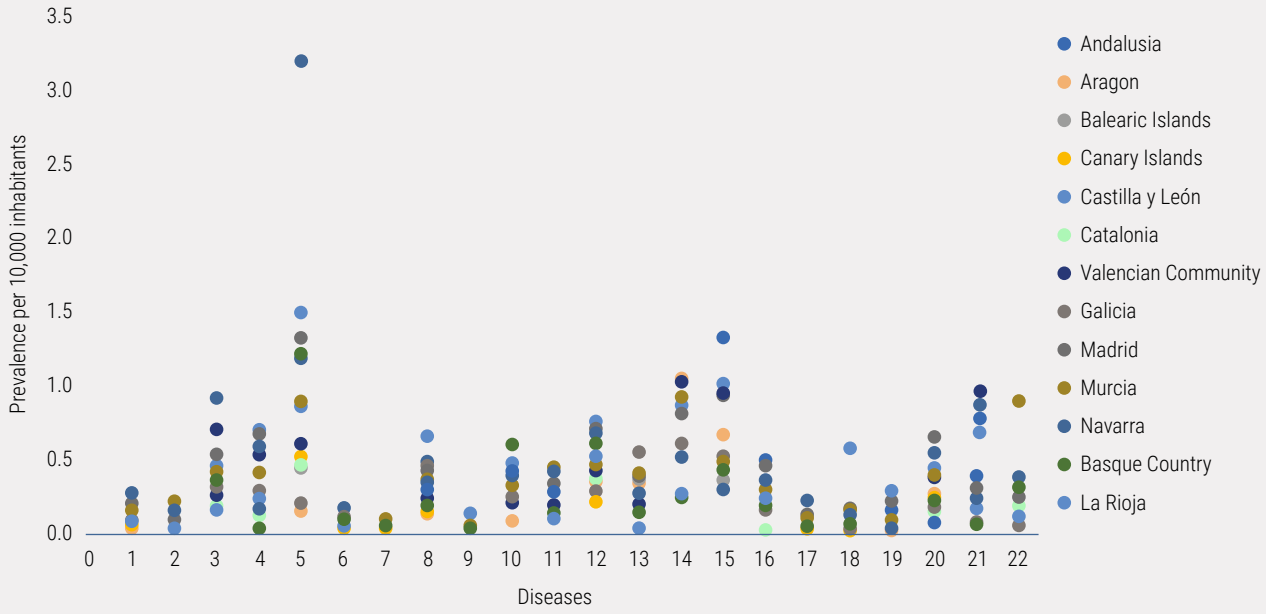
Enrolling a sufficient number of people with rare diseases in a clinical trial is difficult due to the low prevalence of the disease and the fact that patients may be geographically dispersed, especially for ultra-rare diseases[5].

Although 30 million of Europeans (including 3 million Spaniards) suffer from rare diseases[11], each rare disease, as defined by the European Commission, is characterised by 5 or fewer cases per 10,000 inhabitants[12].

The Spanish Rare Diseases Register (ReeR), from the Carlos III Health Institute, has documented a total of 28,397 cases of RDs in Spain up to the 1 January 2022. This represents approximately 1% of the potential cases in the country. These cases correspond to 22 rare diseases representing 0.3% of all known diseases. These conditions have been reported in 13 Autonomous Communities (although 4 Autonomous Communities and 2 Autonomous Cities did not provide complete data)[13].

According to the data available, the prevalence rates of these rare diseases vary in our country, ranging from 0.0040 to 3.1840 cases per 10,000 inhabitants. The average rate is 0.293, while the median is 0.2020, with the first quartile at 0.0910 and the third quartile at 0.3990. These are prevalence rates well below the European Union's upper limit for classifying a case as a rare disease[13].

Figure 5. Prevalence of RDs in Spain, according to Autonomous Regions
(as of 1 January 2022, n=28,397 cases and 22 RDs)



Notes: ***(a)*** *4 ACs and 2 Autonomous Cities did not report complete data.* ***(b)*** *diseases:* ***1:*** *Friedreich's Ataxia;* ***2:*** *Proximal Spinal Muscular Atrophy;* ***3:*** *Tuberous Sclerosis Complex;* ***4:*** *Renal Dysplasia;* ***5:*** *Steinert's Myotonic Dystrophy;* ***6:*** *Fabry Disease;* ***7:*** *Gaucher Disease; 8: Huntington's Disease;* ***9:*** *Niemann Pick Disease;* ***10:*** *Rendu Osler Disease;* ***11:*** *Wilson's disease;* ***12:*** *Amyotrophic Lateral Sclerosis;* ***13:*** *Phenylketonuria;* ***14:*** *Cystic Fibrosis;* ***15:*** *Hemophilia A;* ***16:*** *Osteogenesis Imperfecta;* ***17:*** *Angelman Syndrome;* ***18:*** *Beckwith Wiedemann Syndrome;* ***19:*** *Goodpasture Syndrome;* ***20:*** *Marfan Syndrome;* ***21:*** *Prader Willi Syndrome;* ***22:*** *Fragile X Syndrome.*

Source: *own elaboration based on the State Register of Rare Diseases (2022)*[13]

According to the data provided by the ReeR, 72% of registered RDs patients reside in four ACs, namely Andalusia with 29% of people suffering from RDs, followed by Madrid with 21%, Catalonia 12% and the Valencian Community with 10%. These data seem to indicate a geographical concentration within Spain[13].

Despite this pattern, it is essential to consider that the number of patients varies considerably depending on the disease, ranging from 74 (cases of Niemann Pick disease) to 3,634 (individuals with Steinert Myotonic Dystrophy). It is important to note that only four diseases have more than 2,000 patients in Spain. Given this uneven distribution, the discussion on geographical dispersion becomes relevant. This is particularly important, in the context of recruiting an adequate number of patients for studies and clinical trials, since efforts are needed at a national level to cover all the ACs, or even at an international level[13].

Table 4. Number of cases of RDs in Spain, by Autonomous Community

RD	AN	AR	IB	IC	CL	CAT	CV	G	M	MU	NA	PV	LR	OT	TOT
1	217	4	10	11	48	101	46	23	136	21	18	15	2	-	652
2	136	10	5	26	29	97	66	24	72	31	10	10	1	1	517
3	765	57	33	59	106	135	133	82	353	58	45	74	5	1	1,905
4	581	14	28	49	49	83	262	72	446	60	38	2	5	4	1,689
5	1,001	20	53	115	205	349	301	51	887	132	209	264	47	-	3,634
6	132	-	7	4	11	71	46	26	58	14	6	17	-	-	392
7	69	-	3	1	14	35	19	15	33	14	0	7	-	-	210
8	409	18	47	34	156	265	127	125	288	57	23	41	9	-	1,599
9	16	-	0	2	4	14	4	9	12	6	1	2	4	-	74
10	230	9	36	86	110	276	104	66	267	47	25	130	13	8	1,399
11	226	17	19	26	33	112	86	35	215	65	27	29	3	-	893
12	433	42	44	45	179	263	201	74	474	67	44	131	16	75	2,013
13	322	43	43	35	63	289	96	146	251	59	17	29	1	7	1,394
14	757	138	72	113	202	390	511	163	538	138	33	51	8	32	3,114
15	1.120	88	39	95	242	366	208	139	628	75	62	89	9	18	3,160
16	413	-	18	43	73	10	175	42	305	41	23	40	7	4	1,190
17	89	-	4	4	9	69	25	15	78	15	14	8	-	-	330
18	106	-	0	1	2	28	14	5	104	23	7	9	18	-	317
19	131	1	2	6	14	40	30	7	135	12	2	0	9	-	389
20	448	32	18	50	100	108	186	47	432	57	35	46	2	5	1,561
21	318	13	17	22	29	128	39	17	194	23	15	11	5	2	831
22	288	23	32	10	57	128	34	13	165	133	24	66	3	1	976
n(t)	8,207	529	530	837	1,735	3,357	2,713	1,196	6,071	1,148	678	1,071	167	158	28,397
%(t)	29%	2%	2%	3%	6%	12%	10%	4%	21%	4%	2%	4%	1%	1%	100%

Notes: ***(a)*** *diseases:* ***1:*** *Friedreich's Ataxia;* ***2:*** *Proximal Spinal Muscular Atrophy;* ***3:*** *Tuberous Sclerosis Complex;* ***4:*** *Renal Dysplasia;* ***5:*** *Steinert Myotonic Dystrophy;* ***6:*** *Fabry Disease;* ***7:*** *Gaucher Disease;* ***8:*** *Huntington's Disease;* ***9:*** *Niemann Pick Disease;* ***10:*** *Rendu Osler Disease;* ***11:*** *Wilson's disease;* ***12:*** *Amyotrophic Lateral Sclerosis;* ***13:*** *Phenylketonuria;* ***14:*** *Cystic Fibrosis;* ***15:*** *Haemophilia A;* ***16:*** *Osteogenesis Imperfecta;* ***17:*** *Angelman Syndrome;* ***18:*** *Beckwith Wiedemann Syndrome;* ***19:*** *Goodpasture Syndrome;* ***20:*** *Marfan Syndrome;* ***21:*** *Prader Willi Syndrome;* ***22:*** *Fragile X Syndrome;* ***(b) ACs: AN:*** *Andalusia;* ***AR:*** *Aragon;* ***CAT:*** *Catalonia,* ***CL:*** *Castilla y León and Leon,* ***CV:*** *Community of Valencia,* ***G:*** *Galicia,* ***IB:*** *Balearic Islands,* ***IC:*** *Canary Islands,* ***LR:*** *Canary Islands,* ***LR:*** *La Rioja,* ***M:*** *Madrid,* ***MU:*** *Murcia,* ***NA:*** *Navarra,* ***PV:*** *Basque Country.* ***RD:*** *Rare Diseases.* ***OT:*** *Other (44 Autonomous Communities and 2 Autonomous Cities, which reported incomplete data).*

Source: *Spanish Rare Diseases Register (2022)*[13]

➜ Genetic variability

The diverse aetiology of RDs, resulting from multiple genetic mutations, presents a particular challenge in recruiting a cohort homogeneous enough to participate in a CT[5].

Every year, new genes linked to a variety of rare conditions are identified. In the Orphanet database, these genes are registered and constantly updated as recent scientific research is published. These genes are responsible for one or more diseases and are linked to databases containing information on various mutations[14].

Since 2009, an average of 170 new genes have been registered annually representing a 5% increase in the number of genes registered between 2009 and 2022. Currently, there are a total of 4,440 catalogued genes that are associated with 3,696 rare diseases. Given that Orphanet has identified 6,258 RDs in its catalogue, we could conclude that we just know 60% of the genes associated with currently documented RDs[14].

Case study

Pantothenate kinase-associated neurodegeneration (PKAN)

Let us focus on a concrete example to understand the challenges of selecting a homogeneous cohort of patients with RDs: PKAN.

Due to the variable clinical presentation and progression rates of PKAN, patient selection for clinical trials is challenging. The true prevalence of the disease remains uncertain, with estimates indicating 1-3 cases per million. Diagnosis of PKAN is often delayed and the lack of disease biomarkers further complicates patient identification. The clinical spectrum of PKAN comprises classical and atypical phenotypes, each characterised by a different age of onset, symptoms and disease progression. These differences require personalised approaches to patient selection and study design[15].

Strategies to select patients with RDs such as PKAN involve considering multiple patient cohorts or registry studies. The different classical and atypical phenotypes require separate studies. Classical patients have early onset, rapid progression and movement-related symptoms, while atypical patients have later onset, slower progression and neuropsychiatric features. Therefore, two distinctive studies are needed to better assess treatment efficacy. However, this poses challenges, such as the recruitment of adequately powered subgroups and the risk of contradictory results[15].

The balance between homogeneity and heterogeneity is crucial. The initial study could focus on patients with classic PKAN, as their more rapid progression allows for a more sensitive detection of treatment effect. However, the severity and rapidity of disease progression make it difficult to demonstrate efficacy. Patients with atypical PKAN and slower progression require longer follow-up, which may make it difficult to distinguish between natural variation and treatment effects. This leads to consider post-launch follow-up studies or studies that enable clinical variables to better understand intrapersonal progression rates[15].

Grouping patients in RDs with various phenotypes can be problematic due to the limited number of participants. While some studies enrol all types of patients, this approach may yield heterogeneous results. Alternatively, enrolling all type of patients with the diseases may work when focusing on a close biomarker or conducting non-pharmacological follow-up studies. Ultimately, patient selection strategies in PKAN must carefully balance clinical heterogeneity, disease progression and assessment of treatment efficacy[15].

Challenges in identifying cohorts in the neurodegenerative disease PKAN

- Uncertain prevalence: estimates 1-3 cases/million. Lack of biomarkers makes identification of the disease difficult.
- Clinical spectrum with classical and atypical phenotypes requires personalised approaches. Strategies: multiple cohorts and registry studies. Classical and atypical patients need separate studies.
- The initial study in classical PKAN detects some treatment effects but makes it difficult to demonstrate efficacy. Studies in atypical PKAN patients need prolonged observations, to distinguish natural fluctuations from treatment effects.

Nota: ***PKAN:*** *pantothenate kinase-associated neurodegeneration.*

Fuente: *Videnovic (2023)*[15]

➜ Characterisation of the natural history

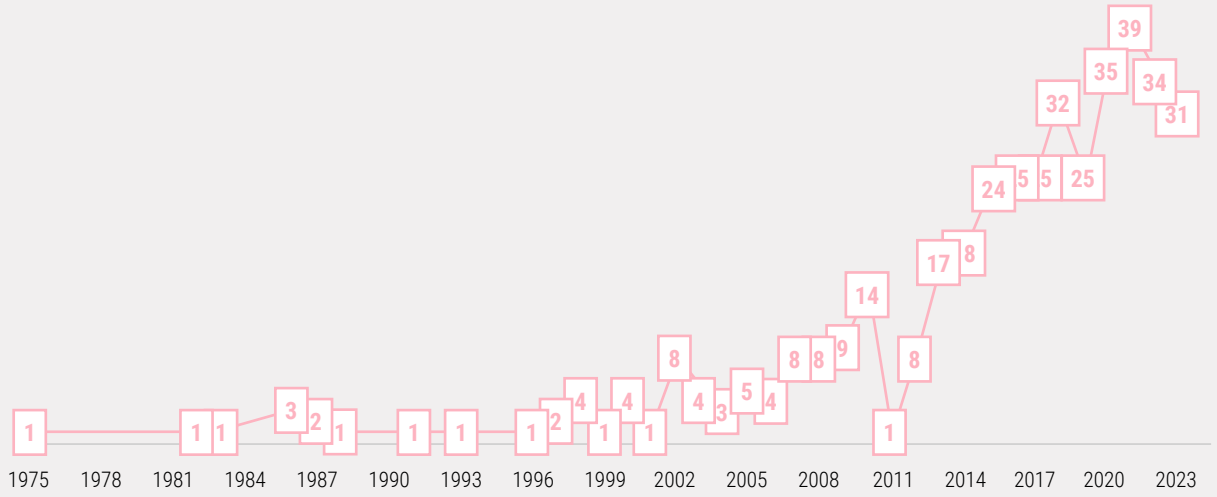
The limited understanding of the natural history of many rare diseases makes it difficult to define relevant targets for clinical trials and to accurately interpret the results obtained[5].

Several studies highlight the importance of understanding the natural history of RDs for the development of OMPs. However, it is clear that for many of these conditions our knowledge in this area remains limited[16-18]. No research has been done to quantify these knowledge gaps. In other words, we still do not know which of the 6,000-7,000 RDs we know in depth and which we barely understand.

Nevertheless, it is undeniable that there is a push for natural history studies in the context of RDs. A prominent example is the FDA initiative to provide guidance to industry through the creation of a guideline entitled "Rare Diseases: Natural History Studies for Drug Development"[19].

In addition, it is important to note that publications disseminating research results on natural history of these diseases have steadily increased in recent years. Between 2000 and 2022, an average increase of 10% in the number of publications has been observed. This translates into a significant increase in scientific output, from an average of 6 publications per year during the period 2000-2010 to 21 publications in the period 2011-2020, and finally to 35 publications between 2021 and 2023, as shown in Figure 6.

Figure 6. Publications of results of natural history studies in RDs



Source: *own elaboration based on Pubmed.*
Search performed on 25 August 2023, using the following criteria: (natural history [Title/Abstract]) AND (rare disease [Title/Abstract])

➜ Lack of suitable animal models

There is a lack of appropriate animal models for several rare genetic disorders, which hampers preclinical research and the assessment of the safety and efficacy of potential treatments. Even where animal models are available, direct extrapolation of findings to humans may be limited[5].

Progress in the development of treatments for RDs relies heavily on safety and efficacy data from animal models at the preclinical stage. However, it is essential that appropriate models are used and that in vivo experiments are designed accurately. Otherwise, the usefulness of the data generated will be limited and the results will lack relevance for clinical application[20].

Unfortunately, it has been observed in a considerable amount of research that the use of unsuitable mouse models negatively affects the quality of the studies[20]. An illustrative example can be found in the case of the TDP-43[III] transgenic model for amyotrophic lateral sclerosis (ALS). In the initial presentation of the model, scientists at the University of Washington identified distinctive features of ALS and attributed the lethality of the model to motor neuron degeneration[22], which generated great enthusiasm among the scientific community as it offered an alternative to previous transgenic models based on the Superoxide Dismutase mutation which were widely used for ALS research. Several investigations began using this mouse line to evaluate compounds in the pre-clinical phase[20]. However, it was found that the characteristic lethality of TDP-43 mice was not linked to motor neuron dysfunction or degeneration, as initially believed, but was due to intestinal obstruction[23]. This finding underlines the importance of using appropriate animal models and careful interpretation of preclinical results to ensure effective and reliable translation of findings into future clinical applications.

In this context, the International Mouse Phenotyping Consortium (IMPC) project becomes relevant. The IMPC is an international effort led by 21 research institutions, with the aim of identifying the function of every protein-coding gene in the mouse genome. To achieve this, the IMPC is systematically inactivating or knocking out each of the approximately 20,000 genes that make up the mouse genome. Mice with inactivated/nulled genes are then subjected to standardised physiological tests (phenotyping tests) in various biological systems to infer gene function, before the data are made available to the research community. As of July 2023, inactivation/cancellations have already been generated for more 10,000 genes. More than 8,400 of these inactivation/deletions had been phenotyped, generating more than 100 data points and more than 700,000 images[24].

Finally, among the various animal species, rats, mice and birds constitute almost 90% of the animals used for research purposes[25]. However, the growing re-awareness of animal sentience and their capacity to experience pain and suffering has led to strong opposition to animal research among many scientists and the general public. Due to these concerns, the use of animals in research is declining in areas where alternative in vitro or in silico methods are available[25]. In the field of RDs, the use of zebrafish as an alternative to the mouse model is on the rise[26].

➜ Resource constraints

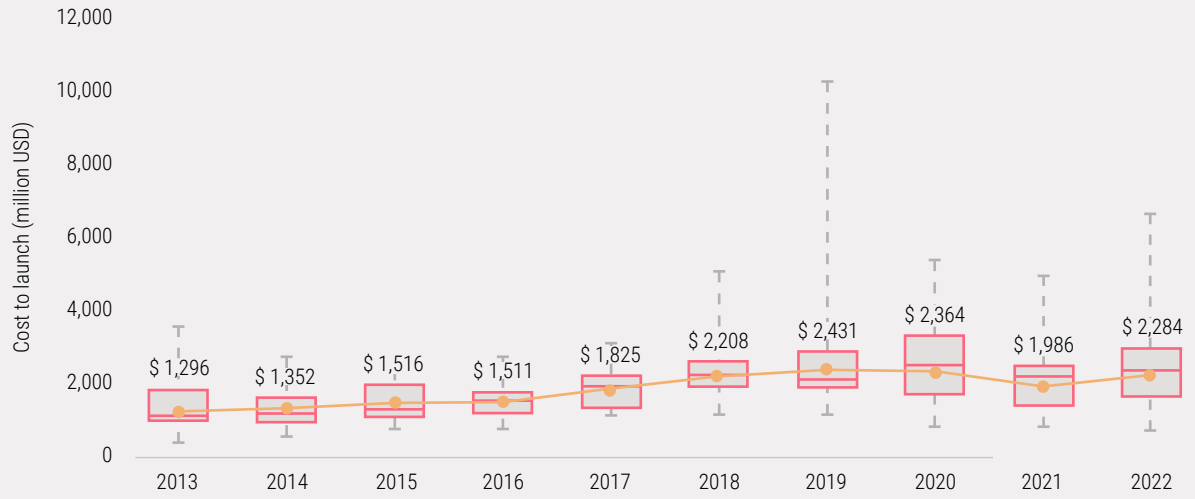
Clinical trials to address RDs are costly and time consuming, and many smaller biotech and pharmaceutical companies may lack the resources to undertake such initiatives[5].

We do not have data related to specific R&D expenditures for OMPs. However, we do have a large amount of information on R&D expenditures for medicines in general. This information could provide insight into the costs involved in the production of an innovative medicine.

In 2022, the top 20 pharmaceutical companies spent a total of $139 billion on R&D, with the average cost of developing an innovative drug from discovery to launch at $2.284 , representing an increase of $298 compared to 2021 (Figure 7)[10].

III *43 kDa (kilodaltons) transactivation response DNA-binding protein (TDP-43) is a nuclear protein involved in the regulation of multiple cellular processes, regulating transcription and transport of more than 600 mRNAs*[21]

Figure 7. Average R&D cost for the development of an innovative medicine



Note: *desde el descubrimiento hasta su lanzamiento.*

Source: *Deloitte (2023)*[10]

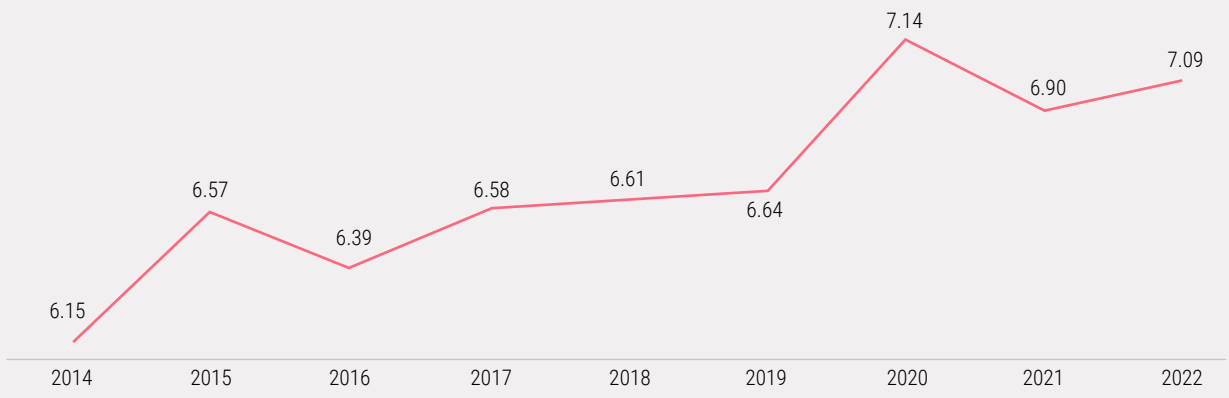
Rational for selecting the Deloitte study is based on the fact that it is the most current data and it covers historical data for the last 10 years. However, a wide range of data related to the R&D costs of new drug development has been published in the literature, ranging from 113 million[27-29] to $6 billion[28-30]. This variation has led to a debate involving mainly two prominent authors. In 2020, Wouters and collegues published a study indicating an average R&D cost of $1.6 billion[31] per new drug, while Dimasi's 2016 research proposed a significantly higher average expenditure of $2.8 billion[30].

The key points related to these discrepancies are based on the following arguments. On the one hand, the allocation of a cost of capital to R&D efforts is questioned, given that the pharmaceutical industry is dedicated exclusively to R&D and the cost of capital should be closer to 0% than 10%. On the other hand, there is a debate about the representativeness of the samples (data from large pharmaceutical companies versus data from small and medium-sized enterprises [SMEs]). The use of proprietary data in comparison with public data is also highlighted, as well as the differences in the specific costs of each stage (pre-clinical and clinical). Finally, the imputation of costs for the development of failed molecules (only 1 in 10,000 molecules investigated are commercialised) is discussed. Taken together, these divergent perspectives highlight the nuances in the assessment of the costs of R&D in pharmaceuticals[28].

In addition, a study by Schuhmacher et al (2023) states that between 2001 and 2020, 16 major pharmaceutical companies invested more than $1.5 trillion into R&D, resulting in the launch of 251 new drugs. On average, each pharmaceutical company invested about $4.4 billion per year in R&D, launching approximately 0.78 novel drugs per year. However, almost half of the companies failed to translate their R&D investments into sufficient commercial value, showing a negative investment-outcome ratio. This has led some companies to counteract this situation through mergers and acquisitions[32].

The average time from the start of Phase I clinical trials to the completion of Phase III trials ("average clinical trial cycle time") in 2022 is 7.09 years, which is broadly in line with previous years, but with an additional year compared to 2014[10] (Figure 8).

Figura 8. Mean cycle time of clinical trials in various therapeutica areas (in years)



Source: *Deloitte (2023)*[10]

➜ Ethical considerations

Rare genetic disorders often affect vulnerable populations, raising ethical dilemmas around the conduct of clinical trials and the administration of experimental treatments in these groups[5].

Although minors do not have the legal capacity to give consent, it is essential to seek their assent by communicating information adapted to their level of understanding. In this context, Ethics Committees play a crucial role, as they require a thorough understanding of the paediatric dimension in order to balance the benefits and inherent risks in research in children[33].

In this sense, the active collaboration of parents and children in the research development process is of significant relevance. Such collaboration not only allows for the needs and preferences of both groups to be addressed but also contributes to the incorporation of key perspectives into the research design and analysis. However, it is important to remember that the absence of legal capacity to consent introduces substantial implications for aspects such as trial design, data analysis, and selection of comparison . Consequently, it is imperative that these trials are conducted by highly trained investigators with a strong paediatric background[33].

Moreover, it is imperative to diligently address the management of factors such as pain, fear, distress and possible separation from parents. In this regard, an efficient prevention and minimisation strategy is required ensuring the emotional and psychological well-being of the children involved. It is important to note that the newborn group is the most vulnerable segment of the paediatric population, implying an even greater need for meticulous and cautious screening during all stages of the research[33].

Key ethical issues in the administration of placebo in CTs related to RDs include[34]:

1. **Consent**: Participants must provide informed consent based on a clear understanding of the potential benefits, risks, uncertainties, and objectives of the trial.

2. **Inclusion**: Ethical decision-making in clinical trials requires the open participation of a diverse set of stakeholders, including experts, patients, ethicists and regulators, to ensure a complete perspective.

3. **Mitigate risks**: The study design should minimise the potential risks associated with placebo administration. This could include limiting the duration of placebo exposure, using primary outcomes based on time to event, and incorporating unequal randomisation to reduce the number of subjects receiving placebo.

➜ Other aspects

Other aspects which will be mentioned in other chapters of this report, include:

Regulatory challenges: The regulatory framework associated with rare genetic disorders is complex, and meeting regulatory requirements in terms of design, data analysis and submission of applications to the relevant authorities is challenging[5].

Low commercial attractiveness: The limited prevalence of RDs has an impact on the market for OMPs, leading to a decrease in the economic incentives that would encourage pharmaceutical companies to invest in the development of these drugs. As a result, R&D costs must be borne by a significantly reduced patient population base[5].

Treatment costs and reimbursement: Certain rare diseases are chronic conditions that require treatment, which can increase the cost of treatment as patients may need to take the medicine for many years. In addition, the reimbursement process for OMPs can be lengthy and complex, making it difficult for patients to access these medicine[5].

Storage and distribution costs: Some OMPs have unique storage and distribution requirements, which can also increase associated costs[5].

Therefore, in contrast to more common pathologies, clinical trials related to RDs tend to be characterised by a sample size, coupled with the difficulty of conducting standard randomisation processes and the implementation of the double-blind approach (neither the patient nor the physician knows whether the drug or placebo is administered). Quantifying disease progression and the choice and use of comparative agents can also be challenging. Finally, it should be noted that trials in RDs generally involve shorter time intervals[3,35–37].

Table 5. Characteristics of clinical trials in rare and prevalent diseases

	Rare diseases				Prevalent diseases			
Source	Bell (2014)[37]	Rana (2018)[35]	Kudyar (2023)[36]	REec (2023)[3]	Bell (2014)[37]	Rana (2018)[35]	Kudyar (2023)[36]	REec (2023)[3]
Sample size	-	96	89	22	-	290	452	76
Randomisation	36%	30%	42%	n.a.	72%	80%	87%	-
Double blind	18%	4%	37%	n.a.	35%	33%	60%	-
Active comparator	22%	30%	54%	36%	43%	80%	59%	56%
Placebo	17%	-	-	31%	27%	-	-	29%
Average trial duration (years)		5.0	-			6.9	-	-
Commercial promoter	-	-	-	90%	-	-	-	70%
Children under 18 years of age	21%			33%	11%			11%

Source: *mentioned in the table*

1.4. Strategies to overcome OMPs research challenges

To address the inherent challenges face by R&D research, novel or alternative approaches are employed in the design of clinical trials, the application of different analytical methods, and the consideration of alternative outcome, such as surrogate variables. Major categories of alternative designs include[38]:

- **Comparison with external or historical controls:** In situations where randomisation to a control group is impractical or ethically inappropriate, single-arm trials are often used to evaluate new therapies. Recently, the comparison of data from outside control subjects with ongoing studies has been explored. This approach involves contrasting cohort characteristics, inclusion criteria, outcome measurement and other factors to ensure meaningful comparisons. Natural history data can also function as external controls but require adjustment for differences.

- **Longitudinal approach designs:** Longitudinal designs take advantage of repeated measurements on the same patients to increase the usefulness of the data and reduce variability. These include self-controlled studies, crossover designs (where patients receive different treatments in sequence) and N-of-1 designs (where individuals receive different treatments over time). Repeated measurements can also improve randomised parallel studies, allowing comparison between treatments cross-sectionally and within subjects.

- **Master protocols:** These innovative approaches evaluate multiple experimental therapies or biomarker-defined populations under one overarching protocol. Platform trials, a type of master protocol, employ shared control arms and multiple experimental arms, leading to greater recruitment efficiency and smaller sample sizes. Basket trials refer to designs in which a targeted therapy is evaluated in multiple diseases that have common molecular alterations. Umbrella trials, on the other hand, evaluate multiple targeted therapies for a single disease that is stratified into subgroups according to molecular alteration. Basket and umbrella trials employ a molecular screening protocol that allows recruitment of different diseases with the same molecular alterations or that differentiates the single disease into different molecular subtypes[39].

- **Adaptive designs:** Adaptive designs allow for adjustment of trial procedures or statistical methods during the study, improving flexibility and efficiency. Adaptive randomisation adjusts randomisation probabilities based on accumulated data. Adaptive dose-finding trials identify maximum tolerable doses more efficiently than traditional methods. Other adaptive designs include sequential cluster designs, sample size re-estimation, hybrid phase I/II and adaptive multiple designs. Proper planning, including early dialogue with regulators, is essential to preserve the integrity of the study and to increase the acceptability and validity of the results obtained.

The main novel analytical strategies used in the context of OMPs research are described below[38]:

- **Causal inference:** When randomisation is not possible, causal inference methods can control bias and provide valid comparisons between new therapies and control groups. These methods are increasingly used in the assessment of benefit-risk evidence during therapeutic development, especially in RDs settings. Causal inference involves estimating treatment effects comparing outcomes observed under different treatments, taking into account potential biases and confounding factors. Strategies such as the "objective trial" framework, the use of a "target trial" framework, the propensity score matching and inverse treatment probability weighting are used to minimise biases. The success of causal inference methods depends on the size of the treatment effect and the sample size.

- **Obtaining evidence from other sources:** This strategy involves integrating information from different sources or populations. Evidence collection could be within a trial with different disease types, across trials, or from adult to paediatric populations. Methods such as hierarchical Bayesian modelling and meta-analytic-predictive approaches facilitate the integration of information. The assumption of interbiability between cohorts or trials is important for these methods, and extensions have been proposed that tailor information gathering according to accumulating evidence.

- Other analytical considerations:
  - **Randomisation-based inference:** Instead of traditional likelihood-based inference, randomisation-based inference uses all possible permutations of treatment assignments to calculate p values. It is resistant to biases caused by time trends and works well with small sample sizes, making it suitable for RDs trials.
  - **Adaptive analytical strategy:** Adaptive designs require corresponding adaptive analytical strategies. For example, if a trial has intermediate decisions to graduate from an effective treatment early, the final analysis should reflect this change.
  - **Sample size assessment:** It is crucial to assess the sample size necessary for the power of the study. Simulations are used, especially in complex designs such as master protocols or those involving evidence gathering.
  - **Pharmacometrics:** An alternative strategy that allows extrapolations of information across populations, potentially making trials more ethical and efficient.

The correct selection of clinical endpoints in medical research also plays a key role in the success of clinical trials. These variables present a diverse range in terms of importance and difficulty of measurement. They range from high-level indicators such as "cure" or overall survival, which act as the gold standard, to intermediate variables such as time to disease progression, which provide insight into the severity and efficacy of treatment. Validation of these variables is particularly complicated when working with small study sizes, where the number of patients is limited[40,41].

In this context, some clinical variables become crucially important. For example, the measurement of renal failure in Fabry disease can have a significant impact on patients' daily life and survival. Achieving symptom improvement and meeting patients' individual preferences is invaluable, even in the absence of direct evidence linking these improvements to disease progression. However, it is imperative to support these improvements with a thorough analysis of how disease and treatment interact with each other. This includes a rigorous assessment of health-related quality of life, especially when patients are facing disability. In this regard, it is necessary to use properly validated scales specific to the disease under investigation[40,41].

When the medical community lacks a solid consensus on which variable is most relevant or when understanding about treatment is still limited, considering multiple variables provides a more complete perspective. However, it is imperative to establish a hierarchy among these variables to avoid confusion and be efficient with the use of resources. In the case of RDs, the use of surrogate variables could provide a more complete picture. However, the evaluation of these variables can be a complex process and sometimes requires stronger evidence support before they are approved by regulatory bodies[40,41].

1.5. Additional considerations about OMPs research

➜ EMA Incentives for OMPs research

OMPs have several institutional support mechanisms to facilitate their development. One of these is protocol assistance, which provides specialised scientific guidance tailored to OMPs, to help sponsors address queries related to studies essential to demonstrate the efficacy, safety and quality of the product[42].

In addition, market exclusivity is extended for authorised OMPs, granting ten years of protection against competitive medicines with similar indications. This duration of protection can be extended by two years for paediatric OMPs[42]. Non-orphan drugs also have a market exclusivity of ten years, limited to generics of the reference product[43].

SMEs also benefit from additional incentives, such as administrative and procedural support from the EMA's office and fee reductions, as they undertake the development of designated orphan drugs[42].

It is important to note that although the EMA does not provide research grants for OMPs sponsors, alternative funding options exist from sources such as the European Union Framework Programmes for Research and Innovation (1984-2013), such as Horizon 2020 (2013-2020), Horizon Europe (2021- 2027), UE ProHealth (2021-2027). Spanish funds are also available, such as the Strategic Projects for Economic Recovery and Transformation (PERTE), which have supported and will continue to support OMPs research through the funding of projects that promote basic and translational research, the development of new therapies and diagnostic tools, among others[44].

➜ Scientific advances in OMPs research

In the field of RDs, scientific advances have led to a diversification of research strategies[5]. Modulation of gene expression also plays a key role, making it possible to generate functional proteins despite mutations. Similarly, monoclonal antibodies are used to target specific pathological processes. Advanced technologies make it possible to precisely influence gene expression[5]. Ultimately, Cell Therapy, which includes haematopoietic stem cell transplantation and gene therapy, is a promising alternative for a number of rare genetic diseases. Drug repurposing also contributes to diversifying therapeutic approaches. These perspectives, ranging from molecular level correction to genomic manipulation, form a broad multidisciplinary landscape in the search for effective therapeutic approaches for rare genetic conditions[5].

➜ Other aspects

Research in RDs encompasses a variety of aspects. The main distinctive elements of R&D in OMPs were discussed in previous sections. However, it is important to mention other areas that also form part of the scope of R&D in this field:

1. **RDs registers:** In Europe, there are 827 RDs registers[45]. A notable example in Spain is the ReeR[46].

2. **Research networks:** Research networks, such as the Centre for Biomedical Networked Research (CIBERER)[47] and European Reference Networks[48], are designed to foster collaboration in R&D, allowing for a more collective and effective approach.

3. **International Rare Disease Research Consortium (IRDiRC):** The IRDiRC[49] which works globally to improve R&D for RDs therapies.

4. **Role of patients and associations:** The active role of patients and the associations that represent them, such as the Spanish Rare Diseases Federation (FEDER)[50], the European Patients' Academy (EUPATI)[51] and the European Association for Rare Diseases (EURORDIS)[52], is essential in RDs research, as they provide valuable perspectives and contribute to informed decision-making.

5. **Incorporation of patient-related outcome measures:** The incorporation of patient-reported outcomes (PROMs) and patient-reported experiences (PREMs) is crucial to assess the real impact of treatments on patients' quality of life. Designing specific tools for RDs improves the accuracy of these assessments[15,53].

6. **Advanced Therapies:** The National Health System (NHS) Plan of Approach for Advanced Therapies aims to facilitate the safe and efficient implementation of these therapies[54].

7. **Artificial Intelligence (AI) in RDs:** AI is revolutionising RDs research by improving diagnosis, prognosis and treatment. However, the generation and use of quality data are essential for its success[55].

8. **Training and information:** Training and information are pillars in RDs research, and recognising clinical genetics as a speciality is a necessary step to foster greater knowledge and a better approach to these diseases[56].

Bibliographic references

1. Orphanet. Orphanet Activity Report. 2022..
2. National Institutes of Biomedical Innovation, Health and Nutrition (NIBIOHN). DDrare: Database of Drug Development for Rare Diseases. Laboratory of Rare Disease Information and Resource Library. Available at: https://ddrare.nibiohn.go.jp/index_e.html.
3. Government of Spain. Ministry of Health. REEC - Spanish Registry of Clinical Studies. Spanish Agency for Medicines and Health Products (AEMPS). [accessed 21 August 2023]. Available at: https://reec.aemps.es/reec/public/web.html.
4. Sun W, Zheng W, Simeonov A. Drug discovery and development for rare genetic disorders. Am J Med Genet A. 2017;173(9):2307-22, doi: 10.1002/ajmg.a.38326.
5. Yoo H-W. Development of orphan drugs for rare disease. Clin Exp Pediatr. 2023, doi: 10.3345/cep.2023.00535.
6. IRDiRC. Orphan Drug Development Guide. Available at: https://orphandrugguide.org/home..
7. McCuistion LE, DiMaggio KV, Winton MB, Yeager JJ. Pharmacology. Chapter 1: Drug Development and Ethical Considerations. 11th edition. Saunders; 2022.
8. MatchTrial. How long does it take to develop a new drug? MatchTrial. 2020, Available at: https://matchtrial.health/en/how-long-does-it-take-to-develop-a-new-drug/.
9. Gupta P, Gupta V, Gupta YK. Phase I clinical trials of anticancer drugs in healthy volunteers: Need for critical consideration. Indian J Pharmacol. 2012;44(4):540-2, doi: 10.4103/0253-7613.99350.
10. Deloitte. Seize the digital momentum. Measuring the return from pharmaceutical innovation 2022. Deloitte Centre for Health Solutions. 2023.
11. European Commission. World Rare Disease Day: 30 million Europeans suffer from more than 6000 different rare diseases. Available at: https://spain.representation.ec.europa.eu/noticias-eventos/noticias-0/dia-mundial-de-las-enfermedades-ra- ras-30-million-Europeans-suffer-more-than-6000-rare-diseases-2022-02-28_en..
12. European Commission. Report from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions. Report on the implementation of the Commission Communication "Rare Diseases: A Challenge for Europe" (COM(2008) 679 final) and the Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02). 2014..
13. Government of Spain. Ministry of Health. Situation of Rare Diseases in Spain. State Register of Rare Diseases (ReeR). 2022.
14. Orphanet. Orphanet: Reports. Available at: https://www.orpha.net/consor/cgi-bin/Education_Home.php?lng=EN.
15. Videnovic A, Pfeiffer HCV, Tylki-Szymańska A, Berry-Kravis E, Ezgü F, Ganju J, et al. Study design challenges and strategies in clinical trials for rare diseases: Lessons learned from pantothenate kinase-associated neurodegeneration. Front Neurol. 2023;14:1098454, doi: 10.3389/fneur.2023.1098454.
16. Haq I, Brashear A. The vital role of natural history studies in rare disease: insights from X-linked dystonia parkinsonism. Brain Commun. 2023;5(3):fcad125, doi: 10.1093/braincomms/fcad125..
17. Ayala A, Cheetham J, Durham T, Maguire M. The Importance of Natural History Studies in Inherited Retinal Diseases. Cold Spring Harb Perspect Med. 2023;13(3):a041297, doi: 10.1101/cshperspect.a041297.
18. Nickel M, Schulz A. Natural History Studies in NCL and Their Expanding Role in Drug Development: Experiences From CLN2 Disease and Relevance for Clinical Trials. Front Neurol. 2022;13:785841, doi: 10.3389/fneur.2022.785841.
19. FDA. Rare Diseases: Natural History Studies for Drug Development. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rare-diseases-natural-history-studies-drug-development.
20. Flora A. The Versatile Mouse Model for Rare Disease Research. Available at: https://www.jax.org/news-and-insights/jax-blog/2019/May/the-versatile-mouse-model-for-rare-disease-research.
21. Martínez González L. Modulación de TDP-43: una nueva estrategia terapéutica para la esclerosis lateral amiotrófica. http://purl.org/dc/dcmitype/Text, Universidad Complutense de Madrid, 2021.
22. Wegorzewska I, Bell S, Cairns NJ, Miller TM, Baloh RH. TDP-43 mutant transgenic mice develop features of ALS and frontotemporal lobar degeneration. Proc Natl Acad Sci U S A. 2009;106(44):18809-14, doi: 10.1073/pnas.0908767106.

23. Hatzipetros T, Bogdanik LP, Tassinari VR, Kidd JD, Moreno AJ, Davis C, et al. C57BL/6J congenic Prp-TDP43A315T mice develop progressive neurodegeneration in the myenteric plexus of the colon without exhibiting key features of ALS. Brain Res. 2014;1584:59-72, doi: 10.1016/j.brainres.2013.10.013.

24. International Mouse Phenotyping Consortium. IMPC Data Release 19.1 Notes. Available at: https://www.mousephenotype.org/data/release.

25. KIANI AK, PHEBY D, HENEHAN G, BROWN R, SIEVING P, SYKORA P, et al. Ethical considerations regarding animal experimentation. J Prev Med Hyg. 2022;63(2 Suppl 3):E255-66, doi: 10.15167/2421-4248/jpmh2022.63.2S3.2768.

26. Crouzier L, Richard EM, Sourbron J, Lagae L, Maurice T, Delprat B. Use of Zebrafish Models to Boost Research in Rare Genetic Diseases. Int J Mol Sci. 2021;22(24):13356, doi: 10.3390/ijms222413356.

27. Light DW, Lexchin JR. Pharmaceutical research and development: what do we get for all that money? BMJ. 2012;345:e4348.

28. DiMasi JA. Research and Development Costs of New Drugs. JAMA. 2020;324(5):517, doi: 10.1001/jama.2020.8648.

29. Rennane S, Baker L, Mulcahy A. Estimating the Cost of Industry Investment in Drug Research and Development: A Review of Methods and Results. Inq J Med Care Organ Provis Financ. 2021;58:469580211059731, doi: 10.1177/00469580211059731.

30. DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: New estimates of R&D costs. J Health Econ. 2016;47:20-33, doi: 10.1016/j.jhealeco.2016.01.012.

31. Wouters OJ, McKee M, Luyten J. Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. JAMA. 2020;323(9):844, doi: 10.1001/jama.2020.1166.

32. Schuhmacher A, Hinder M, von Stegmann Und Stein A, Hartl D, Gassmann O. Analysis of pharma R&D productivity - a new perspective needed. Drug Discov Today. 2023;28(10):103726, doi: 10.1016/j.drudis.2023.103726.

33. European Commission. Ethical considerations for clinical trials on medicinal products conducted with minors. Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use. Revision 1. 2017.

34. Cree BA, Bennett JL, Sheehan M, Cohen J, Hartung H-P, Aktas O, et al. Placebo-controlled study in neuromyelitis optica-Ethical and design considerations. Mult Scler Houndmills Basingstoke Engl. 2016;22(7):862-72, doi: 10.1177/1352458515620934.

35. Rana P, Chawla S. Orphan drugs: trends and issues in drug development. J Basic Clin Physiol Pharmacol. 2018;29(5):437-46, doi: 10.1515/jbcpp-2017-0206.

36. Kudyar P, Konwar M, Khatri Z, Gogtay NJ, Thatte UM. Evaluation of clinical trials done for orphan drugs versus nonorphan drugs in infectious diseasesan eleven year analysis [2010-2020]. Perspect Clin Res. 2023;14(2):56-60, doi: 10.4103/picr.picr_137_21.

37. Bell SA, Tudur Smith C. A comparison of interventional clinical trials in rare versus non-rare diseases: an analysis of ClinicalTrials.gov. Orphanet J Rare Dis. 2014;9:170, doi: 10.1186/s13023-014-0170-0.

38. Li Y, Izem R. Novel clinical trial design and analytic methods to tackle challenges in therapeutic development in rare diseases. Ann Transl Med. 2022;10(18):1034, doi: 10.21037/atm-21-5496.

39. Park JJH, Siden E, Zoratti MJ, Dron L, Harari O, Singer J, et al. Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols. Trials. 2019;20(1):572, doi: 10.1186/s13063-019-3664-1.

40. EMA. Guideline on Clinical Trials in Small Populations. 2006.

41. Zhou BY Yang Song, Yijie. Drug Development for Rare Diseases. New York: Chapman and Hall/CRC; 2023.

42. EMA. Orphan incentives. European Medicines Agency. [accessed 29 August 2023]. Available at:: https://www.ema.europa.eu/en/human-regulatory/research-development/orphan-designation/orphan-incentives.

43. European Commission. Regulation (EC) No 726/2004 of the European Parliament and of the Council, laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. 2004.

44. European Commission. Rare diseases. Available at: https://research-and-innovation.ec.europa.eu/research-area/health/rare-diseases_en.

45. Orphanet. Rare Disease Registries, cohorts and databases. Orphanet Report Series. 2023.

46. Carlos III Health Institute. Rare Diseases State Registry Information System. [accessed 31 August 2023]. Available at: https://reer.isciii.es/.

47. Carlos III Health Institute. Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER). Available at:: https://www.ciberer.es/.

48. European Commission. European Reference Networds. Overview. Available at: https://health.ec.europa.eu/european-reference-networks/overview_en..

49. European Commission. IRDiRC - International Rare Diseases Research Consortium. 2023, Available at: https://irdirc.org/.

50. ERDF. Who are we? Available at:https://www.enfermedades-raras.org/.

51. EUPATI. Education That Empowers. Available at: https://eupati.eu/.

52. EURORDIS. Who we are. Available at: https://www.eurordis.org/who-we-are/our-vision-mission/.

53. Huemer M, Bösch F. Measuring what matters: Why and how to include patient reported outcomes in clinical care and research on inborn errors of metabolism. J Inherit Metab Dis. 2023, doi: 10.1002/jimd.12622.

54. Directorate General for the Common Portfolio of NHS Services and Pharmacy. Monitoring report of the Directorate General for the Common Portfolio of NHS Services and Pharmacy on the Plan for the Approach to Advanced Therapies in the NHS. 2022.

55. Roman-Naranjo P, Parra-Perez AM, Lopez-Escamez JA. A systematic review on machine learning approaches in the diagnosis and prognosis of rare genetic diseases. J Biomed Inform. 2023;143:104429, doi: 10.1016/j.jbi.2023.104429.

56. O'Dowd A. Advanced diagnosis and personalised treatment: the clinical geneticist. BMJ. 2022;377:o1160, doi: 10.1136/bmj.o1160.

Chapter 2

Access and equity in orphan drugs: what makes them unique?

Although current legislation provides safeguards to ensure accessibility and equity in health care, the reality is that there are significant inequalities. The problem of access and equity begins with the lower availability of orphan drugs in Spain compared to other European countries and it is exacerbated by the barriers to access to these treatments that exist in different regions. This is due to the fact that each AC has its own procedures and criteria for authorisation and prescription, in addition to other factors that influence their availability, such as the existence of regional health plans, the number of specialised centres, the number of diseases included in neonatal screening programmes, investment in medicines and participation in clinical trials. In addition to these inequities, there are others related to income level, ethnicity, gender or sexual orientation.

This chapter begins by describing the main regulations in place to promote equity in access to OMPs in Spain, followed by an analysis of the times and levels of access to OMPs that are publicly funded and those that are not, as well as presenting the current situation for advanced therapies. A section is then devoted to exploring regional disparities in the availability of OMPs with a particular focus on the factors that may influence these disparities. Finally, inequity in the care of people with RDs will be addressed.

2.1. Regulation on equal access to OMPs in Spain

Despite the absence of specific legislation regulating RDs-oriented therapies, these drugs are subject to regulatory provisions of varying scope, which emphasise the importance of guaranteeing the universality, quality and safety of medical care, ensuring equal access regardless of the place of residence of the person in need of care. These regulations also prohibit discrimination based on racial or ethnic origin, gender, religion, beliefs, age, disability, sexual orientation or identity, illness or other personal or social conditions.

The General Health Law 14/1986 is a fundamental regulation which establishes general principles, such as the following[1]:

1. Public health care shall be extended to the entire Spanish population. Access to and provision of health care shall be carried out under conditions of effective equality.

2. Health policy shall be geared to overcoming territorial and social imbalances.

In addition, the Law 16/2003, on Cohesion and Quality of the National Health System, indicates that the public health administrations must "ensure citizens' right to health protection, with the common objective of guaranteeing equity, quality and social participation within the NHS". It also establishes (article 24) that "access to healthcare services shall be guaranteed regardless of where in the national territory the NHS users are at any given time, paying special attention to the singularities of island territories". Finally, it emphasises (Article 8) that the healthcare services included in the NHS common basic portfolio "shall be provided in such a way as to guarantee continuity of care, under a multidisciplinary, patient-centred approach, ensuring maximum quality and safety in their provision, as well as conditions of accessibility and equity for the entire population covered"[2].

Furthermore, the Royal Decree 1030/2006, which establishes the portfolio of common services of the National Health System and the procedure for updating it, reinforces the guarantee that "users of the NHS will have access to the portfolio of common services, provided that there is a clinical and health indication for it, under conditions of effective equality, regardless of whether or not a technique, technology or procedure is available in the geographical area in which they reside". It also stresses that "health services that cannot offer any of the techniques, technologies or procedures contemplated in this portfolio in their geographical area shall establish the necessary mechanisms for channelling and referring users who require it to the centre or service where it can be provided, in coordination with the health service that provides it"[3].

On the other hand, the Law 29/2006, on the Guarantees and Rational Use of Medicines and Health Products, recognises the right of all citizens to obtain medicines under equal conditions throughout the NHS, without prejudice to rationalise their prescription and use adopted by the Autonomous Regions. It prohibits the unilateral imposition of specific restrictions on the prescription, dispensing and financing of medicines or health products by the AC[4].

The Law 39/2006, on the Promotion of Personal Autonomy and Care for Dependent Persons, emphasises "universal access for all dependent persons, in conditions of effective equality and non-discrimination", including "the assessment of people's needs, taking into account criteria of equity to guarantee real equality", as well as the "personalisation of care, taking special account of the situation of those who require greater positive action as a consequence of having a greater degree of discrimination or less equal opportunities"[5].

Likewise, the General Public Health Act 33/2011, which includes in its provisions the prevention and early detection of rare diseases, as well as support for people with rare diseases and their families, guarantees that[6]:

1. All persons have the right to equal treatment in public health care without discrimination on the grounds of birth, racial or ethnic origin, sex, religion, belief or opinion, age, disability, sexual orientation or identity, illness or any other personal or social condition or circumstance.

2. Any discrimination between women and men in public health actions is prohibited, in accordance with the provisions of Organic Law 3/2007, of 22 March, for the effective equality of women and men.

3. The disease may not give rise to differences of treatment other than those resulting from the treatment process, from objective limitations on the exercise of certain activities or from those required for reasons of public health.

Finally, article 91.5 of RD-legislative 1/2015, of 24 July, which approves the revised text of Law 29/2006 on guarantees and rational use of medicines and health products, reiterates that "measures aimed at rationalising the prescription and use of medicines and health products that may be adopted by the Autonomous Regions shall not lead to differences in the conditions of access, catalogue and price of medicines and health products financed by the NHS". Similarly, it states that "the right of all citizens to obtain medicines under equal conditions throughout the NHS is recognised, without prejudice to the measures aimed at rationalising the prescription and use of medicines and health products that may be adopted by the Autonomous Regions in the exercise of their powers"[7].

More recently, Act 121/000110 of June 2022 sought to consolidate the equity, universality and cohesion of the NHS[8]. This bill proposed that health services be provided primarily by public entities[8,9], incorporated the consideration of health in all government policies, and expanded access to health care in various situations[I]. The Congress of Deputies gave the green light for this law to go through parliament in September 2022[10], but by September 2023, it had not yet been approved due to several factors, including the electoral process of that year[11,12].

2.2. Analysis of the timing and level of access to orphan drugs

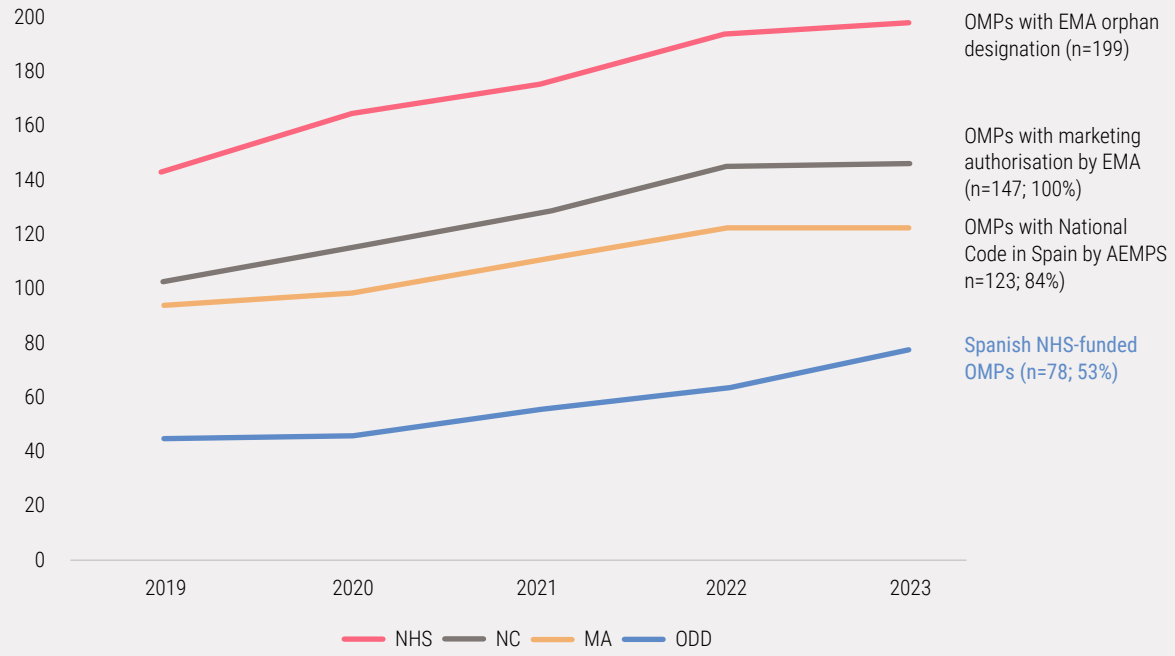
➜ Funded OMPs

One of the key issues in addressing equitable access to medicines relates to the availability of these products. This includes identifying which medicines have received NHS funding following EU approval and the time from approval to availability.

By 2023, the EMA's Committee for Orphan Medicinal Products and Medicinal Products (COMP) had designated more than 1,800 active substances as OMPs. Of these, 199 had the orphan drug designation (ODD), of which 147 medicines had a marketing authorisation (MA) in the European Union. Of these 147, 123 had a national code (NC) assigned by the Spanish Agency for Medicines and Health Products (AEMPS). Finally, of the latter, 78 had been financed by the NHS. Thus, between 2019 and 2023, there were average annual increases of 8.4% in the number of ODD, 9.3% in MA, 7.0% in NC and 14.7% in OMPs funded by the NHS (Figure 1)[13].

I *The right to health care at public expense is recognised for persons in the ascending line who are reunited when they have a son or daughter entitled to health care in the NHS and there is no third party obliged to pay; for Spanish nationals residing abroad during their trips to our country, as well as for their relatives; for applicants for international protection, applicants and beneficiaries temporary protection, and for victims of trafficking in human beings or sexual exploitation. It also guarantees that the right to health protection and healthcare for people who are not registered or authorised as residents in Spain can be exercised under the same requirements and conditions in all the Autonomous Regions.*

Figure 1. Levels of access to OMPs in Europe and Spain, 2019-2023

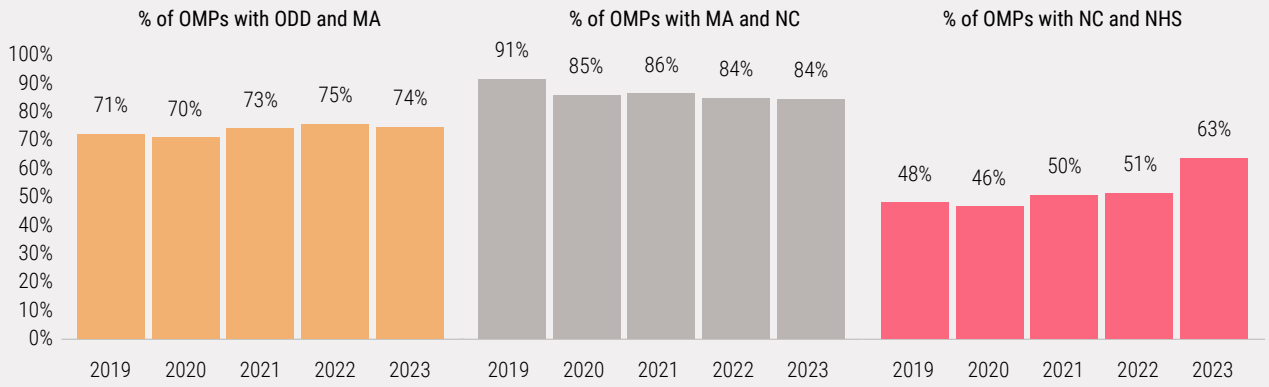


Notes: ***MA:*** *marketing authorization.* ***NC:*** *National Code* ***ODD:*** *Orphan drug Designation.* ***EMA:*** *European Medicines Agency.* ***OMP:*** *Orphan Medicinal Products.* ***AEMPS:*** *Spanish Agency for Medicines and Health Products.* ***NHS:*** *National Health System.*

Source: *AELMHU (2022[14], 2023[13])*

In other words, seven out of ten medicines designated as orphan drugs between 2019 and 2023 are authorised in Europe. Eight out of ten of these authorised medicines are marketed in Spain, but only 63% of nationally coded medicines are funded by the NHS (Figure 2)[13].

Figure 2. Relationship between levels of access to OMPs, 2019-2023

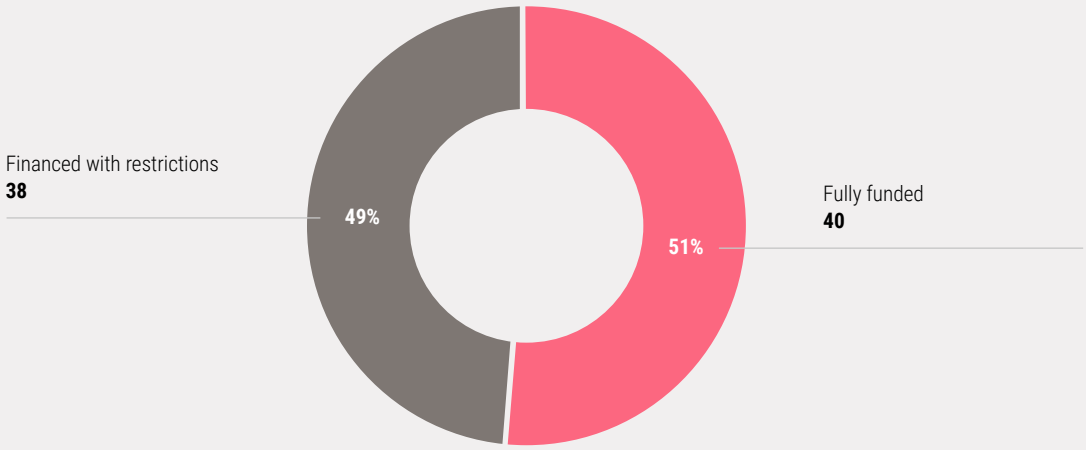


Notes: ***MA:*** *marketing authorisation.* ***ODD:*** *Orphan drug Designation.* ***NC:*** *National Code.* ***NHS:*** *NHS funding*

Source: *AELMHU (2022[14], 2023[13])*

Despite obtaining funding, many OMPs do so with specific limitations. Out of a total of 78 OMPs that currently have favourable price and reimbursement approval in the NHS, 49% (n=38) are under limited funding which may be due to restrictions in the indications for which they are approved or the presence of an indication not included in the funding (Figure 3)[13].

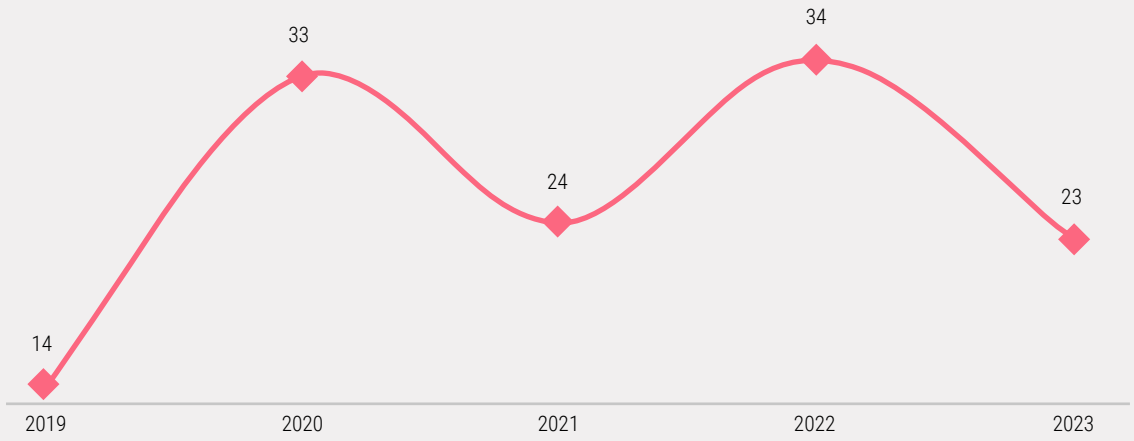
Figure 3. Conditions of the financed ODs, December 2023



Source: *AELMHU (2022[14], 2023[13])*

Regardless of whether the drug is publicly funded, another relevant issue is the length of the whole process. The average waiting time for funding[II] a new OMP in Spain in the period between 2020 and 2023 was 23 and 33 months (2 to 3 years). In 2019, this waiting time was considerably shorter, with a duration of 14 months (Figure 4)[13].

Figure 4. Average waiting time for OMPs funding in Spain, in months, 2019-2023



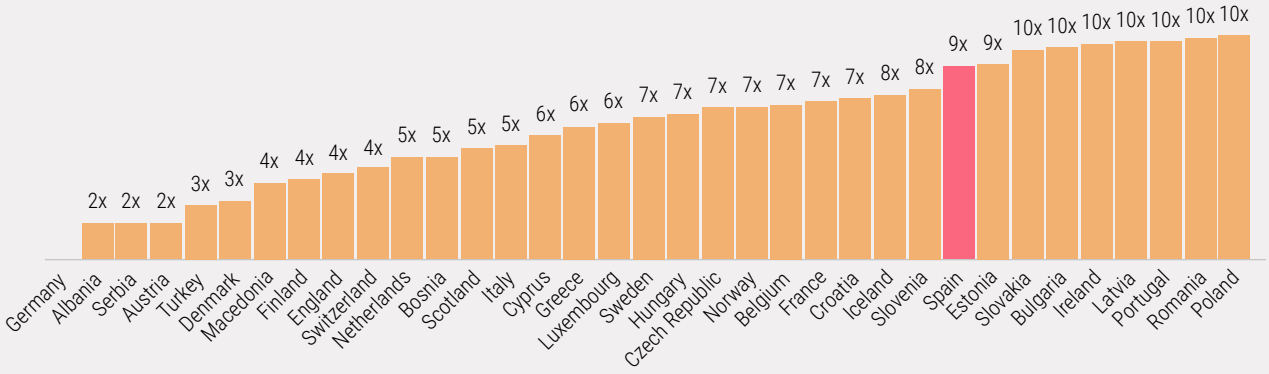
Note: *Average waiting time between obtaining the National Code and the date of discharge to the NHS.*

Source: *AELMHU (2022[14], 2023[13])*

In this context, Spain ranks 27th out of 36 European nations, according to data from the W.A.I.T. report. On average, patients with RDs in Spain have to wait nine times longer than those in the leading country, Germany, to access the pharmacological treatment needed for their condition (Figure 5). It is also worth noting that, for non-oncological RDs, Spanish patients face a wait 10 times longer than in Germany[15].

II *Average waiting time between obtaining the NC and the date of discharge to the NHS.*

Figure 5. European comparison of waiting times for OMPs funding, relative to best country, 2018-2021



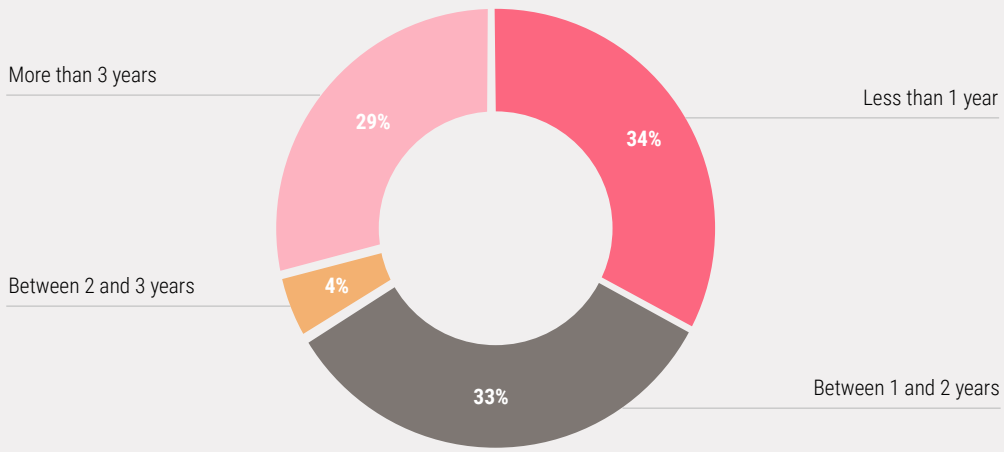
Note: *The graph shows how many times longer a country's waiting time is relative to the lead country, using average waiting times obtaining marketing authorisation and local public funding over the period 2018-2021. Malta has been excluded because it represents an outlier, being the country with the longest waiting times, twenty times longer than Germany. It should be noted any case that in Germany immediate reimbursement is allowed for medicines with no therapeutic alternative, and after 6 months an assessment of the clinical benefit of the drug is carried out, followed by a price negotiation that may take a further 6 months. If the volume of sales exceed 50 million per year, the new negotiated price applies, irrespective of whether the drug is an orphan drug or not.*

Source *IQVIA (2023)*[15]

➜ Non-funded OMPs

In 2023, there were 24 OMPs with a marketing authorisation, but without an assigned national code. In addition, 45 OMPs were identified as having a national code but no public funding. Within the group of the 24 OMPs without a national code, 34% had received their marketing authorisation within the last year, 33% had obtained it between 1 and 2 years ago, 4% between 2 and 3 years ago, and the remaining 29% had obtained it more than 3 years ago (Figure 6)[13].

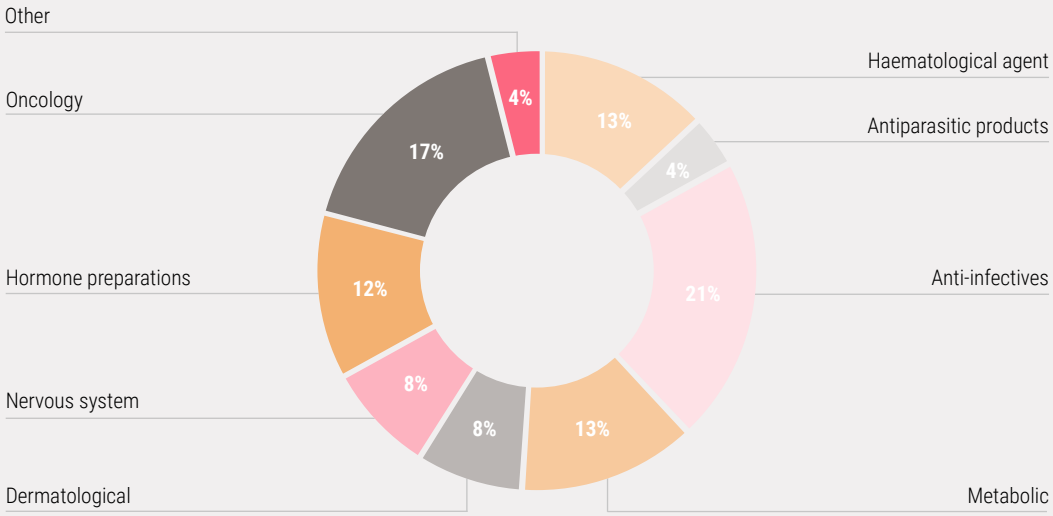
Figure 6. Distribution of OMP without national code by waiting time to marketing authorisation, December 2023 (n=24)



Source: *AELMHU (2023)*[13]

OMPs with a marketing authorisation but without a national code were grouped into five therapeutic areas. These areas included anti-infectives (21%), oncological (17%), haematology and metabolic (13% each one) and hormonal preparations (12%). The remaining percentage was distributed in various areas, such as nervous system, dermatology, anti-parasitic products and others (Figure 7)[13].

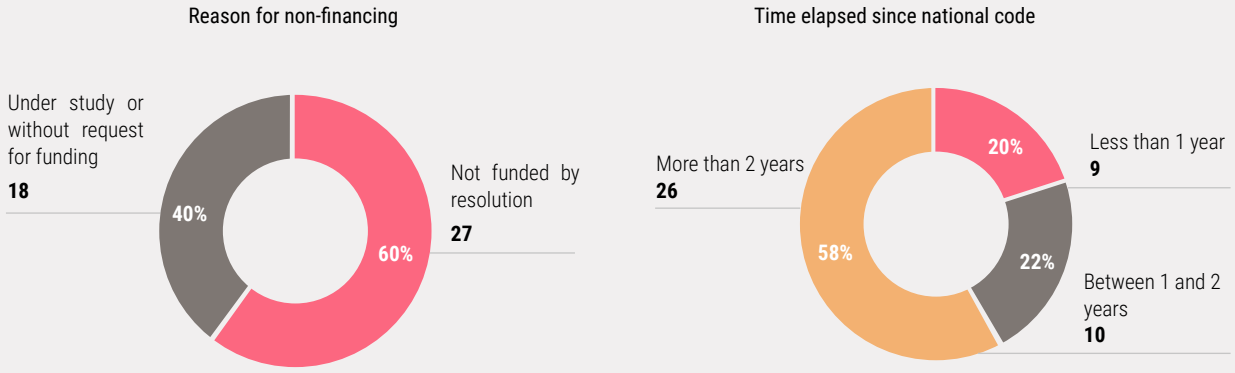
Figure 7. Therapeutic areas of OMPs with marketing authorisation and without national code, December 2023 (n=24)



Source: *AELMHU (2023)*[13]

Of the 45 OMPs with a national code but not funded by the NHS, 27 had not received approval for funding due to a resolution[III], while 18 were under study or had not been applied for funding. Of the 45 nationally coded and unfunded OMPs, 20% had obtained their national code within the last year, compared to 22% which had obtained their code between 1 and 2 years ago. The remaining 58% had obtained their code more than 2 years ago (Figure 8)[13].

Figure 8. Reasons for non-financing and waiting times, nationally coded and unfunded OMPs, December 2023

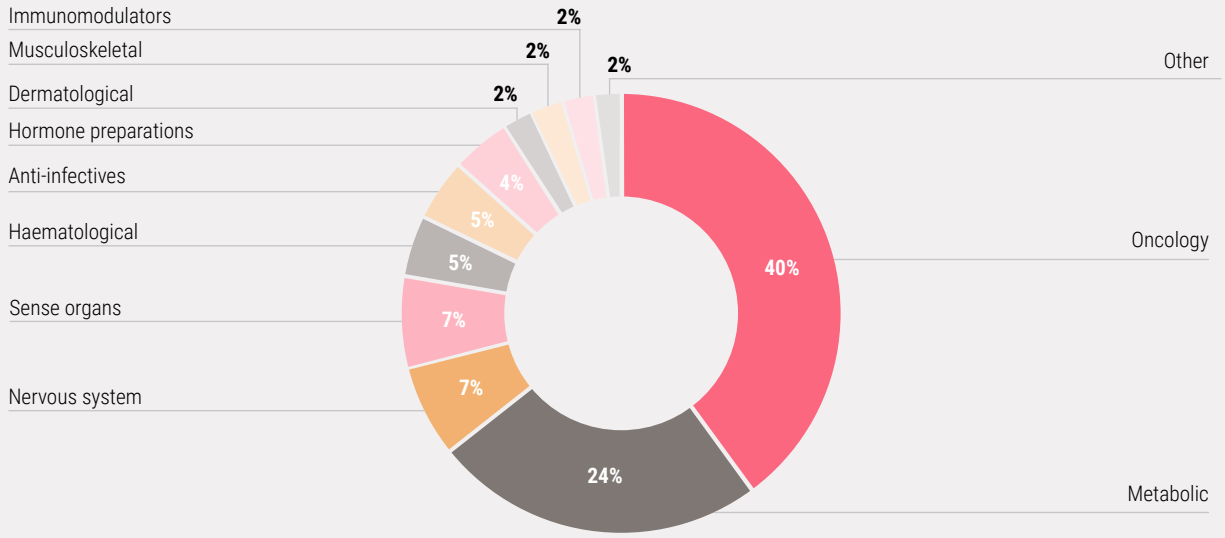


Fuente: *AELMHU (2023)*[13]

Forty percent of the 45 NC and unfunded OMPs were dedicated to oncology, followed by 24% to metabolic medicines, 7% to nervous system and sense organs, 5% to haematological and anti-infectives, and 4% to hormonal preparations. The remaining non-funded OMPs are indicated in the areas of dermatology, musculoskeletal, immunomodulators and other specialities[13].

III *Although we do not have data for December 2023, as of March 2022, there were 28 OMPs in this situation. In 11% of cases (3), the laboratory had not requested a price. In 32% (9), therapeutic alternatives were available at lower cost. In 39% (11) no price was requested due to uncertainty of clinical benefit, and the proposed price also had a high budgetary impact, not corresponding to the clinical value provided, so that the impact in terms of rationality and distributive justice in the context of the use of clinical resources was adverse. 18% of cases (5) had not been included in the pharmaceutical benefit due to rationalisation of public expenditure and high budgetary impact*[16].

Figure 9. Therapeutic areas of the OMP with national code and without funding

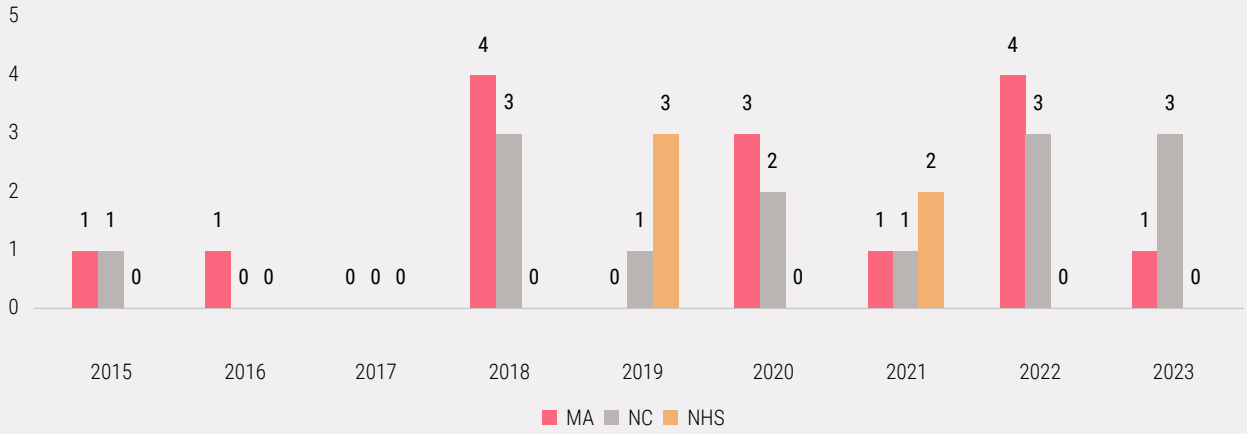


Source: *AELMHU (2023)*[13]

➜ Advanced therapies

Advanced therapies (innovative medicines based on genes, tissues or cells) are associated with very significant improvements in the health and quality of life of patients, including in some cases curing diseases for which there are no therapeutic alternatives in advanced stages. Many of these advanced therapies are considered orphan drugs, due to the low prevalence of their target patient groups, being a specific case of interest. As of 31 December 2023, there were 15 advanced therapies with MA in Europe, of which 14 with CN and 5 funded by the NHS (3 of them funded in 2019 and 2 in 2021) (Figure 10)[13].

Figure 10. Funding status of advanced therapies, Europe and Spain, 2015-2023



Notes: ***MA:*** *marketing authorisation.* ***NC:*** *National Code.* ***NHS:*** *NHS funded.*

Source: *AELMHU (2023)*[13]

2.3. Regional disparities in orphan drug availability

Once a medicine has been publicly funded, it is crucial to understand the extent to which its availability and use varies at the regional level. In many cases, disparities arise, as each region sets its own criteria for the use and prescription of these medicines, at regional, provincial and even hospital level.

Unfortunately, studies on the availability and use of funded medicines at the regional level are virtually non-existent. In addition, we lack databases that provide detailed information on the use of each medicine in specific hospitals and ACs. Therefore, in this section, we will use proxy indicators that allow us to assess regional disparities in access. These indicators will include elements such as the existence of regional plans, the availability of Reference Centres, Services and Units (CSUR), the extent of neonatal screening coverage at regional level, pharmaceutical expenditure by AC and the involvement of each AC in clinical trials related to RDs.

Case study

Spinal muscular atrophy (SMA) 5q

SMA is an inherited neurodegenerative disease caused by mutations in the SMN1 gene, resulting in a deficiency of the survival motor neuron protein. This deficiency causes degeneration of alpha motor neurons in the spinal cord, which triggers symptoms of weakness and progressive decrease in muscle mass. In Spain, approximately 900 people suffer from SMA[17].

Before drug treatments were developed, this disease was the leading genetic cause of mortality in children under 2 years of age. The vast majority of patients (97%) have the 5q[IV] gene-associated type of SMA. Currently available pharmacological treatments to address this disease include nusinersen (licensed by the EMA in 2017 and funded by the National Health System in 2018), the onasemnogene abeparvovec (EMA: 2020; NHS: 2021) and risdiplam (EMA: 2021, not funded by the NHS[V])[17].

A study conducted by García-Parra (2022) focused on investigating access to drugs to treat 5q SMA. The primary purpose of this research was to identify possible disparities in access to these treatments in four ACs in Spain: Andalusia, Castilla-La Mancha, Catalonia and Murcia[17].

The results of the study indicated that several factors may influence the variability of access to treatment, such as the number of centres, services or reference units (CSUR) available, the existence of regional plans for RDs, the implementation of pilot neonatal screening programmes, hospital pharmaceutical spending at the regional level, the participation of the Autonomous Regions in clinical trials related to SMA, and the personal and logistical resources for the clinical management of the disease[17].

There were no significant differences observed in access to nusinersen between the ACs studied. The period between prescription and administration of the drug varied between 7 and 60 days in all the ACs. Catalonia was the AC with the longest time lag between prescription and administration of nusinersen. In addition, it was noted that Catalonia was the only region in which the onasemnogene abeparvovec had been prescribed until 30 June 2022. Table 1 below presents the main findings analysed by the authors[17]:

1. **Available CSUR:** Despite being the Autonomous Region with the highest number of CSUR, Catalonia experienced the longest waiting times for access to nusinersen. This delay was probably due to the complexity of the process, which require an assessment by an expert committee composed of medical and pharmaceutical professionals appointed by the competent authority.

IV *The name 5q comes from the fact that mutations in the SMN1 gene (motor neuron survival gene) are found on chromosome 5.*

V *At the time of the Garcia-Parra study (2022), which is the case study used in this section, it was only available in Spain in open clinical trials and as expanded access. Of the three existing SMA modificator drugs, only two had a published pharmacoclinical protocol (nusinersen in 2018 and onasemnogen abeparvovec in 2022), while risdiplam still did not have one as of 30 June 2022. For this reason, access was only analysed for two drugs: nusinersen and onasemnogen abeparvovec*[17].

2. **Existence of regional plans for RDs:** Of the four ACs studied, only two had regional plans for RDs. However, only the Murcia experts interviewed indicated that their usefulness was relevant.

3. **Implementation of pilot neonatal screening programmes:** Neonatal screening for this disease is available as a pilot programme in the AC of Valencia (Hospital Universitari i Politècnic La Fe in Valencia, from 2021) and in Andalusia (Hospital Virgen del Rocío in Seville, from 2021, and Hospital Regional de Málaga, from 2022). Therefore, only Andalusia (25% of the ACs studied) had a pilot neonatal screening programme for SMA.

4. **Hospital pharmaceutical expenditure at regional level:** Murcia has the highest hospital expenditure per capita (183.45€), followed by Catalonia (172.71€), Castilla-la Mancha (166.66€) and Andalusia (151.11€).

5. **Participation of the ACs in clinical trials:** Two of the four ACs studied, Andalusia and Murcia, were involved in clinical trials related to SMA.

6. **Personal and logistical resources for the clinical management of the disease:** No differences were found in the availability of personal and logistical resources for the clinical management of SMA, as the clinical experts interviewed in the four ACs stated that these resources were available.

Table 1. Time, degree of access and other SMA variables

	Andalusia	Castilla-la Mancha	Catalonia	Murcia
Time and degree of access				
Average time to administration of nusinersen, since prescription (days)	7	7-60	60	30-60
Average time to administration of onasemnogen abeparvovec, from prescription (days)	Not administered	Not administered	15-21	Not administered
Variables analysed				
Nº. of new SMA diagnoses per year	3-4	1-2	4-6	2
Number of neuromuscular RDs reference centres, services or units	1	0	4	0
Existence of regional plans for RDs	Yes	-	-	Yes
Nº. of neonatal screening pilot centres	2	0	0	0
Hospital pharmaceutical expenditure at regional level (2021, thousands of euros)	1,280,296	341,584	1,340,805	278,570
Hospital pharmaceutical expenditure per capita (euros)	151.11	166.66	172.71	183.45
Participation in SMA clinical trials	Yes	No	No	Yes
Availability of personnel and logistical resources for the management of the SMA	Yes	Yes	Yes	Yes

Source: *García-Parra (2022)*[17]

➜ Analysis of factors that may influence access to OMPs in Spain

In the absence of specific studies and without a clear understanding of access to OMPs, various variables, such as the availability of CSUR, the implementation of regional plans for RDs, the implementation of neonatal screening programmes, drug spending and the participation of the Acs in clinical trials related to RDs, may be useful to understand possible disparities in access that may exist between the different ACs.

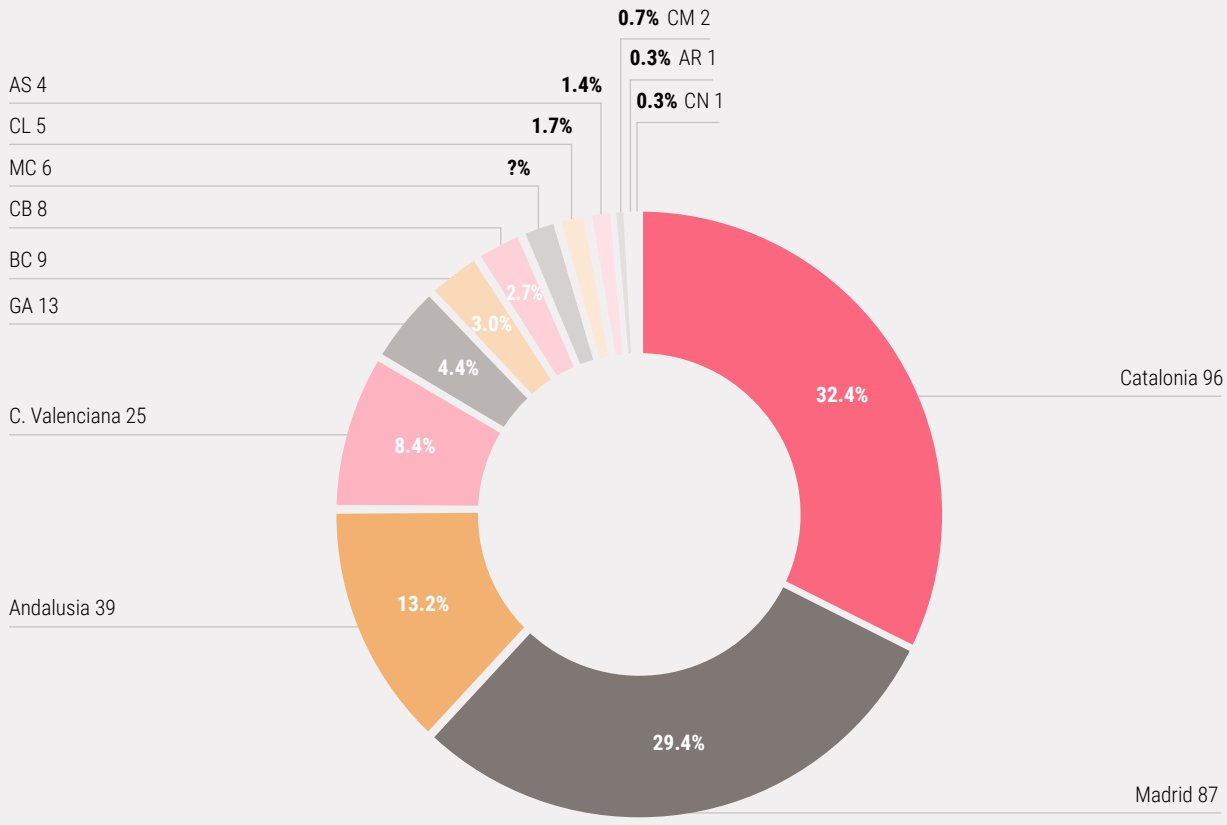
Regional plans

Despite the absence of specific legislation regarding treatments for rare diseases, a strategic framework has been established in 2009, which was updated in 2014. In addition, eight ACs (Andalusia [2008[18]], Madrid [2016[19], to be updated in 2023[20]], Extremadura [2004[21], 2010[22], 2019[23]], Navarra [2017[24]], Murcia [2018[25]], Galicia [2021[26]], Canary Islands [2022[27]] and Castilla y León [2023[28]]) have approved their own plans for RDs. On the other hand, four others (Catalonia, Basque Country, Valencian Community and Castilla la Mancha[29]) have incorporated specific measures to address RDs in their health plans[29].

CSUR

In May 2022, there were a total of 296 CSUR in Spain. However, most of these centres were located in three specific ACs: Catalonia led with 96 CSUR (32.4%), followed by Madrid with 87 (29.4%) and Andalusia with 39 (13.2%) (Figure 11)[30].

Figure 11. Distribution of CSUR by Autonomous Community (n=296), 2022

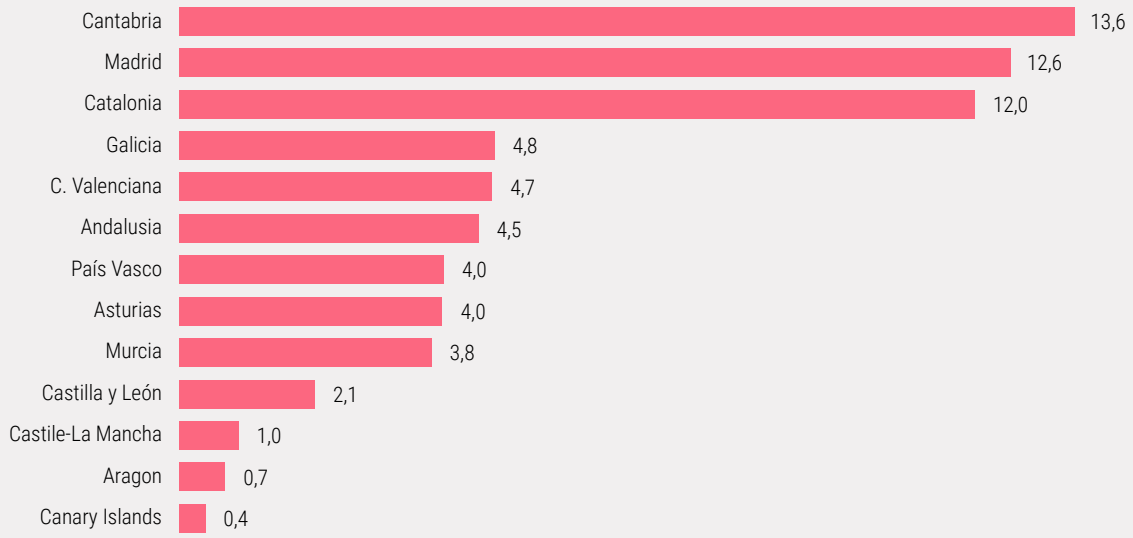


Notes: ***CSUR:*** *Reference Centres, Services and Units.* ***AC:*** *Autonomous Communities.* ***GA:*** *Galicia.* ***BC:*** *Basque Country.* ***CB:*** *Cantabria.* ***MC:*** *Murcia.* ***CL:*** *Castilla y León.* ***AS:*** *Asturias.* ***CM:*** *Castile-La Mancha.* ***AR:*** *Aragon.* ***CN:*** *Canary Islands.*

Source: *Ministry of Health (2022)*[30]

On the other hand, if we analyse the number of CSUR per million inhabitants, we observe that Cantabria has the highest ratio, with 13.6 CSUR per million inhabitants, followed by Madrid with 12.6 and Catalonia with 12.0. Other regions, such as Galicia, the Valencian Community, the Basque Country, Asturias and Murcia, had between 4 and 5 CSUR per million inhabitants. In contrast, 4 ACs (Balearic Islands, Rioja, Navarre and Extremadura) had no CSUR at all (Figure 12)[30].

Figure 12. CSUR per million inhabitants, 2022



Note: ***CSUR****: Centros, Servicios y Unidades de Referencia.*

Source: *Ministry of Health (2022)*[30]

These 296 CSUR were distributed across 47 healthcare centres[VI]. The hospitals with the largest number of CSURs were Hospital Vall D'Hebron in Catalonia, Hospital Sant Joan de Déu in Catalonia and Hospital Universitario de La Paz in Madrid, with 34, 30 and 29 CSURs, respectively. In addition, 7 other hospitals had a significant number of CSUR, ranging from 12 to 24 in each. The remaining centres (a total of 47) had less than 10 CSURs , with 14 of them having only 1 CSUR (Table 2)[30].

Table 2. Distribution of CSUR in the top 10 (out of 47) health care facilities, 2022

CSUR	AC	n	%
Hospital U. Vall D'Hebron	Catalonia	34	10.7%
Sant Joan de Déu Hospital	Catalonia	30	9.4%
La Paz Hospital	Madrid	29	9.1%
Hospital U. Virgen del Rocío	Andalusia	24	7.5%
Hospital Clínic de Barcelona	Catalonia	21	6.6%
Hospital U. y Politécnico La Fe	Valencian Community	21	6.6%
Hospital General U. Gregorio Marañon	Madrid	12	3.8%
Hospital U. 12 de Octubre	Madrid	12	3.8%
Hospital U. de Bellvitge	Catalonia	12	3.8%
Hospital U. Ramón y Cajal	Madrid	12	3.8%

Note: ***CSUR****: Reference Centres, Services and Units. In some cases, a CSUR may be associated with two centres. When we split these centres into two separate entities, the total number of CSUR increases from 296 to 319.*

Source: *Ministry of Health (2022)*[30]

VI *In some cases, a CSUR may be associated with two centres. When we split these centres into two separate entities, the total number of CSURs increases from 296 to 319.*

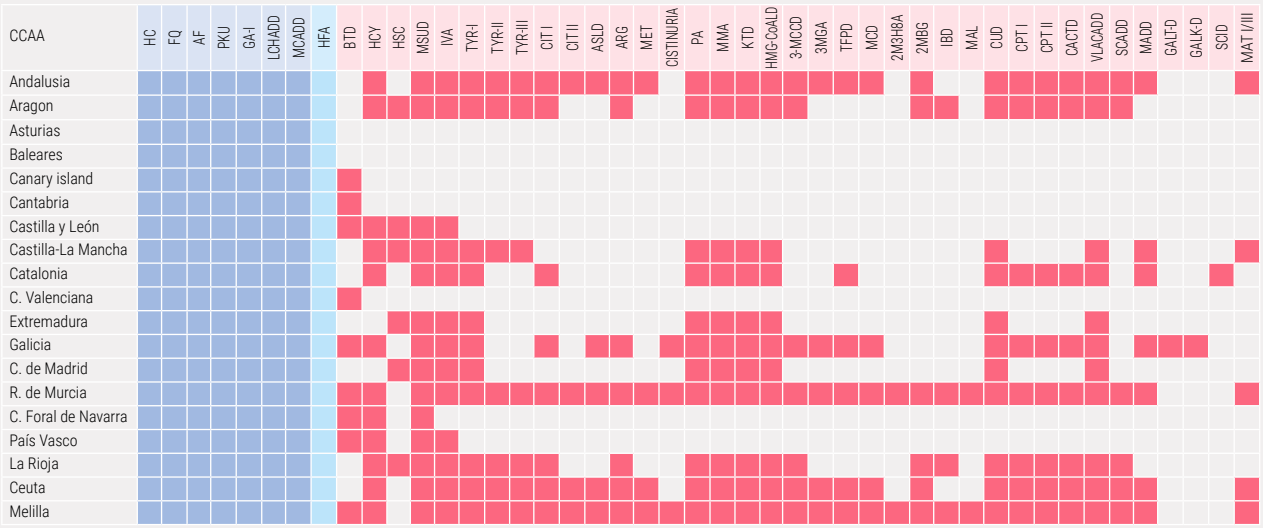
Newborn screening

Newborn screening is an essential part of medical care for newborns, being an effective tool in the early detection and management of rare diseases that, if not detected in time, could lead to irreversible sequelae and even compromise the life of those affected. This type of early detection plays a fundamental role in addressing the impact of RDs, given that approximately 72% of them have a genetic origin and around 70% of them manifest themselves during childhood[31].

In Spain, the decentralisation of health competencies means that each autonomous community has autonomy to manage its health programmes, including newborn screening. This decentralisation generates significant differences in disease coverage between different regions of the national territory. According to the latest information published by the Ministry of Health (in the year 2021), seven diseases are part of the newborn screening programme (NSP) of the common portfolio of health care services of the NHS, and are therefore offered to all newborns in Spain: congenital hypothyroidism (CH), phenylketonuria (PKU), cystic fibrosis (CF), medium-chain acyl-coenzyme A dehydrogenase deficiency (MCADD), long-chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency (LCHADD), glutaric acidemia type I (GA-I) and sickle cell disease (SCD)[32].

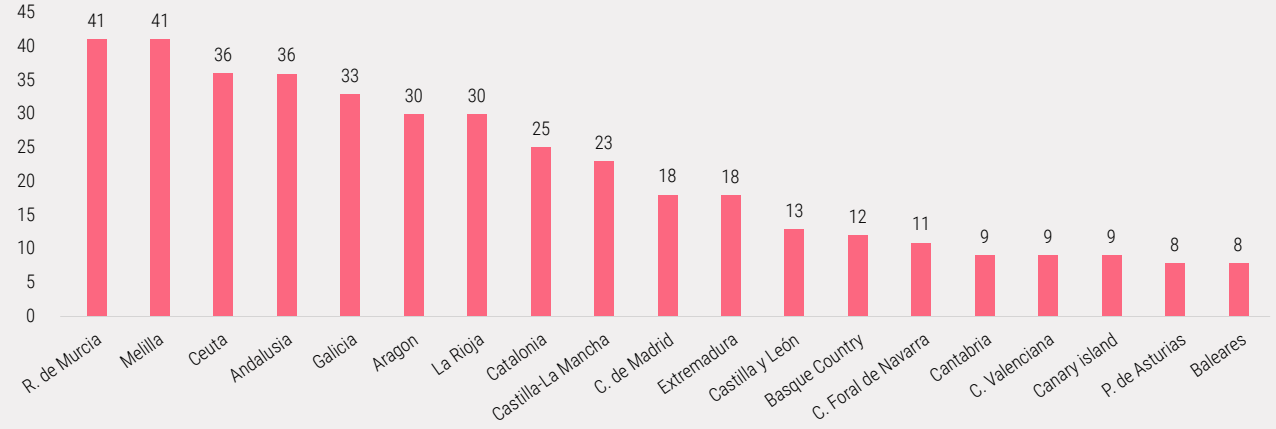
At the regional level, most of the ACs and the two autonomous cities have officially incorporated other diseases into their NSP as part of their respective complementary service, which results in some Spanish regions having up to 41 diseases in their screening programmes by 2021, with Murcia, Melilla, Ceuta, Andalusia, Galicia, Aragon, La Rioja and Catalonia standing out in this respect, while others, such as Asturias and the Balearic Islands only cover eight (Figure 13).

Figure 13. Newborn screening programmes in Spain, 2021



Screening programme of the NHS common portfolio | Diagnosed disease in screening process | Screening programme of the complementary portfolio of the ACs

Note: Some ACs in the screening process diagnose cases of other diseases such as alpha-thalassaemia, beta-thalassaemia, hyperthyrotropinemia, chylothorax, Di George syndrome, other congenital immunodeficiencies, formiminoglutamic aciduria, vitamin B12 deficiency.



Abbreviations ***2M3HBA****: 2-methyl-3-hydrobutyric aciduria;* ***2MBG:*** *2-methylbutyrylglycinuria deficiency;* ***3-MCCD:*** *3-methylcrotonyl-CoA carboxylase deficiency;* ***3MGA:*** *3-methylglutaconic aciduria;* ***FA:*** *sickle cell anaemia;* ***ARG:*** *argininaemia;* ***ASLD:*** *arginosuccinic aciduria;* ***BTD:*** *biotinidase deficiency;* ***CACTD:*** *carnitine/acylcarnitine translocase deficiency;* ***CC.AA. and CA:*** *Autonomous Community;* ***CiA:*** *Autonomous City; CIT-I and* ***CIT-II:*** *citrullinaemia type I and* ***CIT-II:*** *citrullinaemia type I and* ***CIT-II:*** *citrullinaemia type I and CIT-II. II, respectively;* ***CPT I*** *and* ***CPT II:*** *carnitine palmitoyl transferase deficiency type I and II, respectively;* ***CUD:*** *primary carnitine deficiency;* ***CF:*** *cystic fibrosis;* ***GA-i:*** *glutaric acidemia type I;* ***GALK-D:*** *galactokinase deficiency galactosemia;* ***GALT-D:*** *galactosemia due to galactokinase deficiency;* ***GALT-D:*** *galactosemia due to galactokinase deficiency;* ***GALK-D:*** *galactosemia due to galactose deficiency;* ***GALK-D:*** *galactosemia due to galactose deficiency;* ***GALK-D:*** *galactosemia due to galactose deficiency sa-1-phosphate uridyltransferase;* ***HC:*** *congenital hypothyroidism;* ***HCY:*** *homocystinuria;* ***HFA:*** *hyperphenylalaninemia/tetrahydropterin cofactor defect;* ***HMG-CoALD:*** *3-hydroxy-3-methylglutaric aciduria;* ***HSC:*** *congenital adrenal hyperplasia;* ***IBD:*** *isobutyryl-CoA dehydrogenase deficiency (IBD);* ***IVA:*** *isovaleric acidemia;* ***KTD:*** *ketothiolase deficit;* ***LCHADD:*** *long-chain 3-hydroxyacyl-CoA dehydrogenase deficit;* ***MADD:*** *ketothiolase deficit;* ***LCHADD:*** *long-chain 3-hydroxyacyl-CoA dehydrogenase deficit: isovaleric acidemia;* ***KTD:*** *ketothiolase deficiency;* ***LCHADD:*** *long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency; MADDmultiple acyl-CoA dehydrogenase deficiency;* ***MAL:*** *malonic aciduria;* ***MAT I/III:*** *methionine adenosyltransferase I/III deficiency;* ***MCADD:*** *medium-chain acyl-CoA dehydrogenase deficiency;* ***MCD:*** *multiple carboxylase deficiency;* ***MET:*** *hypermethioninaemia;* ***MMA:*** *methylmalonic acidemia;* ***MSUD:*** *maple syrup urine disease;* ***PA:*** *propionic acidemia;* ***PKU:*** *phenylketonuria;* ***SCADD:*** *short-chain acyl-CoA dehydrogenase deficiency;* ***SCID:*** *severe combined immunodeficiency;* ***TFPD:*** *trifunctional protein deficiency;* ***TYR-I, TYR-II*** *and* ***TYR-III:*** *tyrosinemia types I, II and III, respectively;* ***VLCADD:*** *very long-chain acyl-CoA dehydrogenase deficiency;* ***NHS:*** *National Health System.*

Source: *Ministry of Health (2024)*[32]

On 16 April 2024, the Ministry of Health presented measures to the Council of Ministers to expand the basic common portfolio of NHS services in neonatal screening. The approval of tyrosinaemia type 1 and the inclusion of other screenings such as congenital heart disease and hypoacusis were highlighted. The first pathologies to be included will be endocrine-metabolic (n=4), followed by others that will be examined during the second half of 2024 (n=6). By the first quarter of 2025, five pathologies are expected to remain to be evaluated, bringing the total number of diseases included in the common portfolio of services to 23[33].

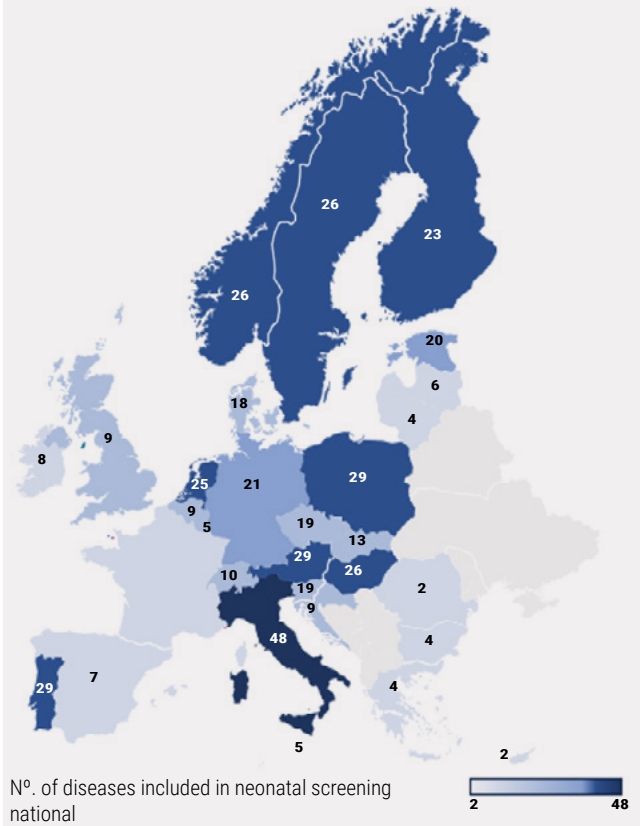
Similarly, in recent years various Acs have expanded the range of diseases included in their NSP. Here are some examples:

- Asturias has included 11 diseases[34].
- Cantabria has included 11 diseases, among which homocystinuria (HCY), MSUD and isovaleric acidemia (IVA) screening which were added in November 202235. Furthermore, it has announced the addition of new diseases during 2024[36].
- Castilla-La Mancha has included 27 diseases[37].
- The Community of Madrid has included a total of 21 diseases and has also added two pathologies to the neonatal screening programme that are in the pilot phase: SMA and severe combined immunodeficiency (SCID)[38].
- The Autonomous Community of Navarre has included a total of 26 diseases[39].
- The Valencian Community announced the incorporation of new diseases in December 2021[40] and subsequently further additions have been announced, bringing the total number of diseases to 11[41].
- Galicia has included a total of 34 diseases among which the incorporation of SMA stands out, as announced in its Official Journal in November 2023[42]. In addition, it has announced the inclusion of new diseases in 2024[43].
- The Region of Murcia continues to lead among the ACs with the highest number of diseases covered by screening as it has included a total of 44 diseases[44].
- Balearic Islands have announced the incorporation of new diseases during 2024[36].

Internationally, Spain ranks as one of the European countries with the lowest number of diseases included in the national NSP considerably behind countries such as Italy (with 48), Poland, Austria or Portugal (all with 29), among others (Figure 14).

Phenylketonuria (PKU) and congenital hypothyroidism (CHT) are frequently included in NSP in all European countries[15]. Both diseases have a relatively high incidence compared to other screened diseases (both have an incidence more than 1 in 10,000, while other diseases included in the programmes may have incidence rates as low as 1 in 250,000)[16]. However, there are other diseases with similarly high incidence rates, such as spinal muscular atrophy (SMA) and sickle cell disease (SCD), which are screened nationally in less than 30% of countries[45].

Figure 14. Number of diseases included in European neonatal screening programmes at the national level



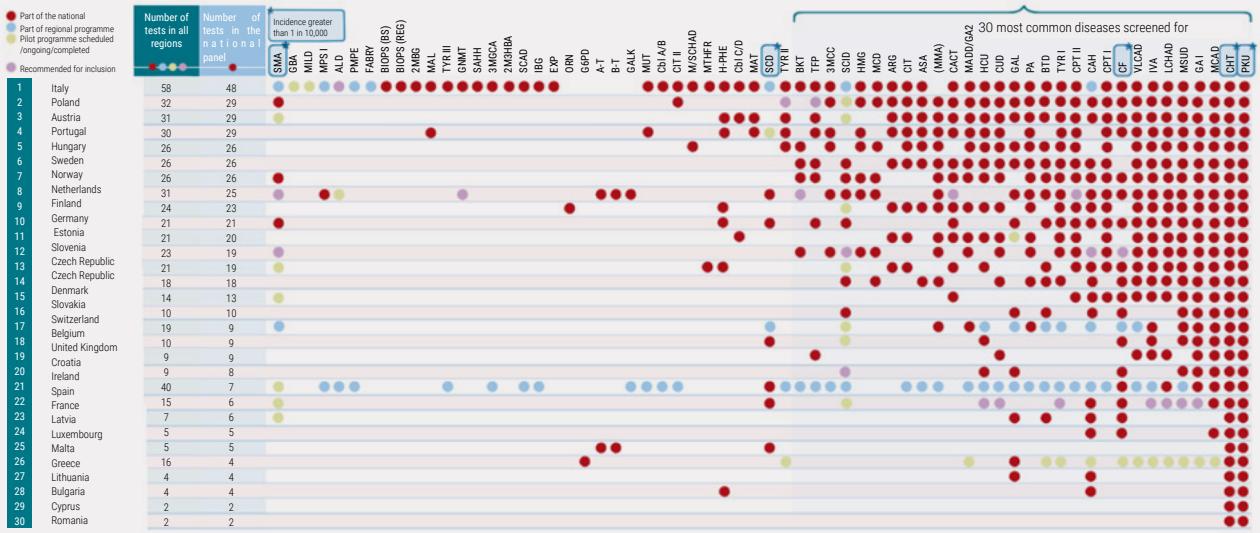
Note: *The figure represents the number of diseases included in the NSPs at national level, excluding those that may be established by regions and/or autonomous communities, as is the case in Spain.*

Abbreviations: ***NSP:*** *Newborn Screening Programme.*

Source: *own elaboration based on data from Charles River Associates (2021)*[15]

Finally, it is observed that, on average there 20% more diseases included in the NSP at regional level than in NSP implemented at national level. Spain is the country with the most marked difference (7 at national level, 40 at regional level) (Figure 15).

Figure 15. Map of disease inclusion in newborn screening panels in 30 European countries



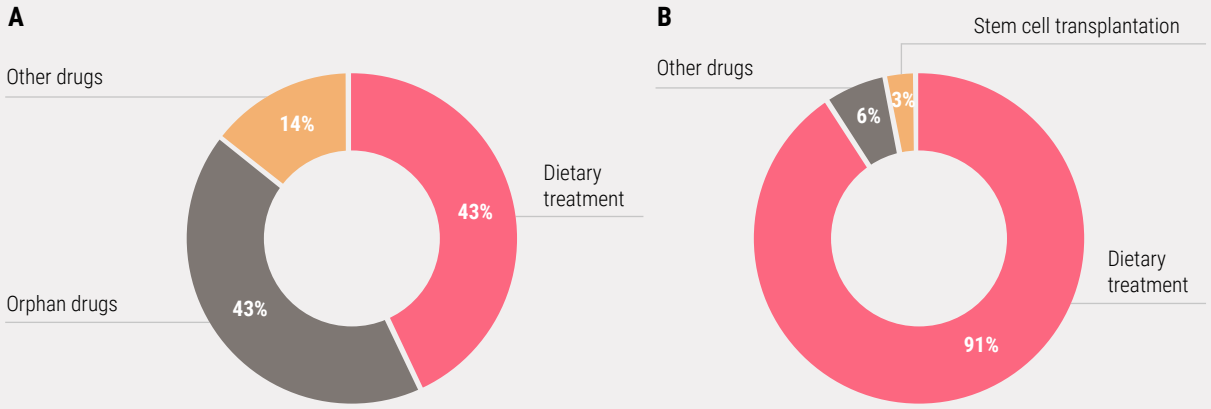
Abbrevations: ***2M3HBA:*** *2-methyl-3-hydroxy butyric aciduria;* ***2MBG:*** *2-methylbutyryl-CoA dehydrogenase deficiency;* ***3MCC:*** *3-methylcroto-nyl-CoA carboxylase deficiency;* ***3MGCA:*** *3-methylglutaconic aciduria;* ***ARG****: argininosuccinic aciduria;* ***ASA:*** *argininosuccinic aciduria;* ***A-T:*** *alpha-thalassaemia;* ***BKT:*** *beta-ketothiolase deficiency: Argininosuccinic aciduria;* ***ASA:*** *argininosuccinic aciduria;* ***B-T:*** *beta-thalassaemia;* ***BTD:*** *biotinidase defect;* ***CAH:*** *congenital adrenal hyperplasia;* ***CF:*** *cystic fibrosis;* ***CHT:*** *cystic fibrosis;* ***CHT:*** *congenital hypothyroidism: Congenital hypothyroidism;* ***CIT:*** *Citrullinaemia type I;* ***CIT II:*** *Citrullinaemia type II (citrin deficiency);* ***CPT I:*** *Carnitine palmitoyl-transferase (L);* ***CPT II:*** *Carnitine palmitoyl-transferase II deficiency;* ***CUD:*** *Carnitine transport deficiency; EXP: Short-chain acyl CoA dehydrogenase deficiency;* ***GA I:*** *Glutaric acidemia type I;* ***GA2:*** *Glutaric acidemia type II;* ***GAL:*** *Galactosemia;* ***GALK:*** *Galactokinase deficiency;* ***GBA:*** *Gaucher disease;* ***HCU:*** *Homocystinuria (CBS deficiency);* ***IBG:*** *Isobutyryl-CoA dehydrogena-se deficiency;* ***IVA:*** *Isovaleric acidemia;* ***LCHAD:*** *Short/medium chain 3-OH acyl-CoA dehydrogenase deficiency;* ***MADD:*** *Multiple acyl-CoA dehydrogena-se deficiency;* ***MAL:*** *Malonic aciduria;* ***MAT:*** *Methionine adenosyltrans- pherase deficiency;* ***MCAD:*** *Medium-chain acyl-CoA dehydrogenase deficiency;* ***MCD:*** *Multiple carboxylase deficiency;* ***MMA:*** *Vitamin B12 deficiency;* ***MPS I:*** *Mucopolysaccharidosis type I;* ***MSUD:*** *Maple syrup urine disease;* ***MUT:*** *Methylmalonic acidemia;* ***OTC:*** *Ornithine transcarbamylase deficiency;* ***PA:*** *Propionic acidemia;* ***PKU:*** *Phenylketonuria;* ***POMPE:*** *Pompe disease;* ***SCD:*** *Sickle cell disease;* ***SCID:*** *Severe combined immunodeficiency;* ***SMA:*** *Spinal muscular atrophy;* ***TYR I:*** *Tyrosinemia type I;* ***TYR II:*** *Tyrosinemia type II;* ***TYR III:*** *Tyrosinemia type III.*

Source: *Charles River Associates (2021)*[45]

It is worth noting the relationship between NSP and the availability of treatments for the diseases being screened. On the one hand of the 81 drugs designated as orphan drugs that are approved and marketed in Spain as of January 2024, only 5% are indicated for any of the diseases included in NSPs. These are orphan drugs for CF (ezacaftor and ivacaftor, and the triple combination of tezacaftor, ivacaftor and elexacaftor) and for SMA (nusinersen and onasemnogen abeparvovec).

On the other hand, among the 7 diseases included in the national NSP, 43% of them have associated OMPs, while the other 43% of the pathologies have a dietary approach. In turn, of the other 33 diseases included in the neonatal screening in some Autonomous Communities, most of them (91%) have an associated dietary treatment, while 6% have a drug indicated for this pathology and only one pathology (3%) requires stem cell transplantation (SCID) (Figure 16). In short, there are few OMPs associated with the diseases that are the object of neonatal screening in Spain, but the diseases with associated OMPs are actually included in the national NSP. In this regard, it should be noted that the orphan drug voxelotor has been approved in Europe for SCD, but is not yet approved in Spain[47].

Figure 16. Approach to the diseases targeted by neonatal screening in the national programme (A) and the diseases included at regional level in some Autonomous Regions (B)



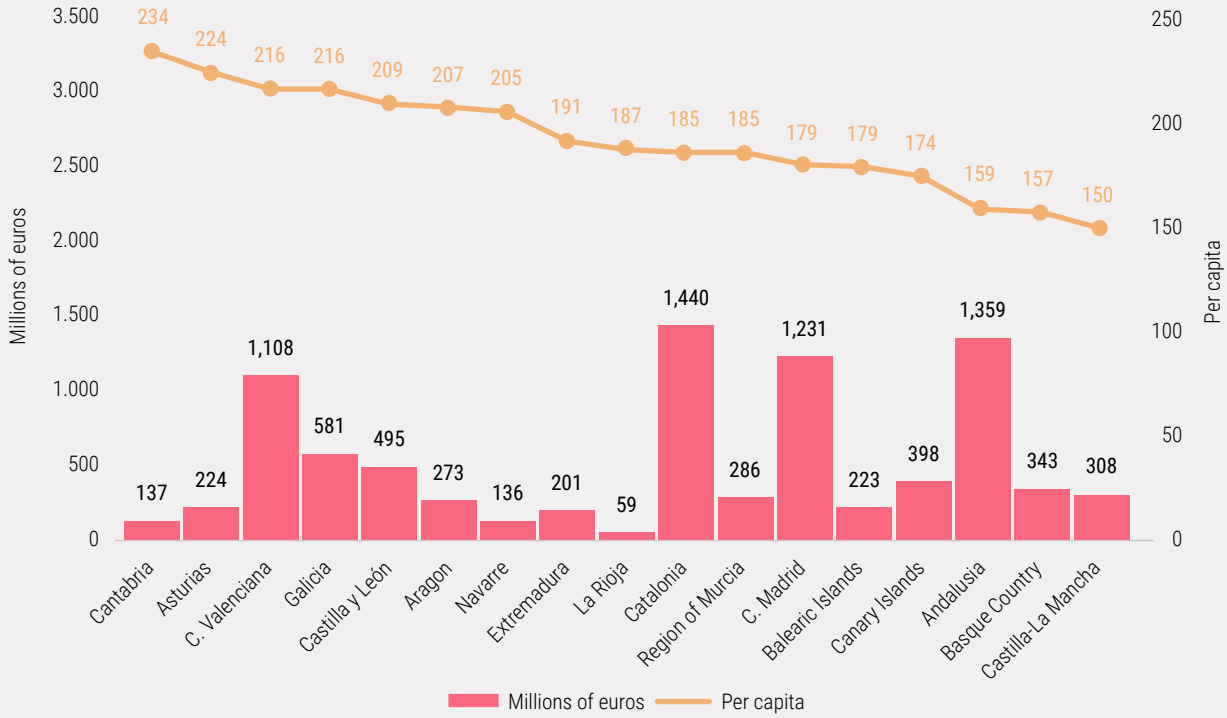
Note: *A) Other drugs include levothyroxine for congenital hypothyroidism (CH). B) Other drugs include corticosteroids for congenital supra-renal hyperplasia (CRH) and oral biotin supplements for biotinidase deficiency (BTD)..*

Sourc: *own elaboration based on Ministry of Health (2019)[32] y CIMA[48]*

Hospital pharmaceutical expenditure

The Autonomous Regions with the highest hospital pharmaceutical expenditure, exceeding Û200 per inhabitant by the end of 2022, include Cantabria (€234), Asturias (€224), the Valenciana community (€216), Galicia (€216), Castilla y León (€209), Arag—n (€207) and Navarra (€205). Hospital pharmaceutical expenditure per inhabitant varies between Û150 and Û234 across Spain, which represents a difference of 56% between the Autonomous Regions with the lowest and the highest expenditure. It is also worth noting that the three Autonomous Regions with the highest total expenditure in this area. Catalonia (1,440 million euros), Andalusia (1,359 million euros) and Madrid (1,231 million euros), are among the 50% of the Autonomous Regions that spend the least per capita (Figure 17)[49,50].

Figure 17. Hospital pharmaceutical expenditure, millions of euros and per capita, December 2022



Sources: *Ministry of Finance and Civil Service (2023)[35] and INE (2023)[36]*

Participation in clinical trials

As highlighted in the research chapter of this report, of the 332 centres currently conducting clinical trials in RDs, approximately 60% are concentrated in three ACs: Catalonia (27%), Madrid (17%) and Andalusia (14%). This distribution is similar to that mentioned earlier in the chapter related to CSURs[51].

2.4. Other orphan drug equity challenges

Although the regulatory framework theoretically guarantees the right to equal access to health products and services including access to OMPs, in practice disparities may arise due to discrimination based on various factors, such as income level, racial or ethnic origin, gender, religion, beliefs, age, disability, sexual orientation, gender identity, or other personal or social conditions or circumstances.

Stigmatisation in health care for people with RDs

The mere fact of living with an RD is in itself a major challenge in terms of access to health care. According to a qualitative study in the United States of 378 people affected by 178 different types of RDs, almost half of them (46%) reported experiencing some form of stigma in the health care setting. This translates into a perception that, among other things, health professionals show a lack of interest and do not provide necessary support, accurate diagnoses, essential resources or adequate treatment[52].

Although the context is very different from that of Spain, some of the testimonies of US patients living with RDs are illustrative. They are often discouraged by the lack of understanding and deficiencies in the health care system. Some expressed: "Providers are not aware about it. There is no effective treatment... Health professionals look down on you or even call you a liar". Other study participants shared their experiences of being labelled as hypochondriacs or being misdiagnosed as anxious by providers who considered their concerns to be psychosomatic in origin[52].

At the most severe end of the spectrum, stigma in medical care was described as a matter of life and death. One participant who was diagnosed with a rheumatic disease 27 years ago lamented: "I almost died twice because previous doctors refused to learn about my diseases.... One doctor left me permanently disabled... A second doctor didn't listen to me... and left me unable to sit. In short, as expressed by one participant: "If I had followed my doctors' recommendations, I would have died several times"[52].

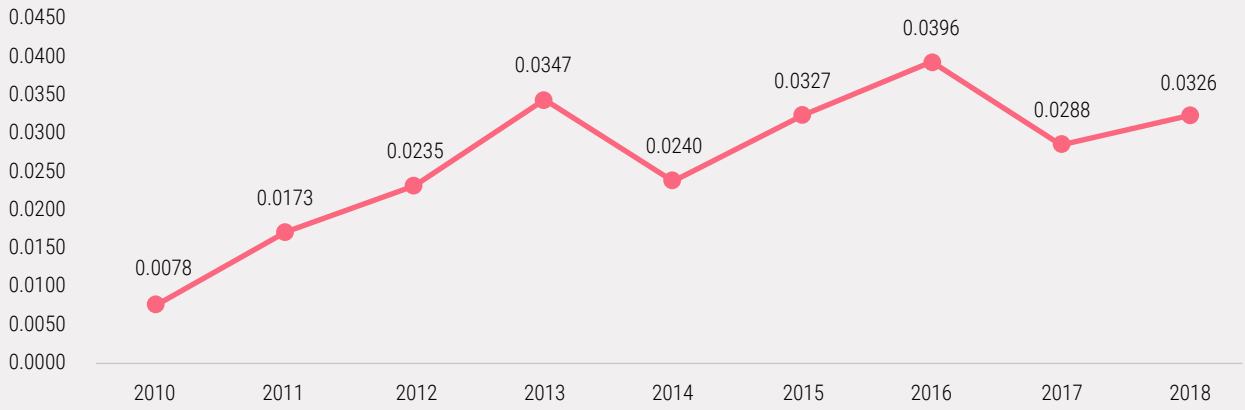
People with "hidden" RDs (those whose symptoms or clinical manifestations are not visible) are more likely to mention healthcare stigma in their responses (55.1%), compared to participants with visible RDs (35.4%)[52].

Inequity in hospital care utilisation and level of admissions

In the context of equity in health care, horizontal equity refers to the principle that people with the same health needs, should have equal access to health care services. The Health Inequity Index (HI) is used to measure differences in access to health care services when health needs are similar[53].

A study conducted in Korea between 2010 and 2018 found that patients with RDs and high-income levels used more inpatient healthcare services than low-income patients[53].In Figure 18, values above 0 indicate that there is a trend in favour of the richest: the inequity index in hospital utilisation increased from 0.0078 in 2010 to 0.0326 in 2018, which means, in other words , that inequity in hospital utilisation due to income level increased fourfold[53].

Figure 18. Horizontal inequality index (HI), relationship between income level and hospital care utilisation, Korea, 2010-2018



Note: *In the horizontal inequity index, values greater than 0 indicate that there is a bias in favour of the wealthier - that patients with higher income levels utilise more hospital care services than patients with lower incomes.*

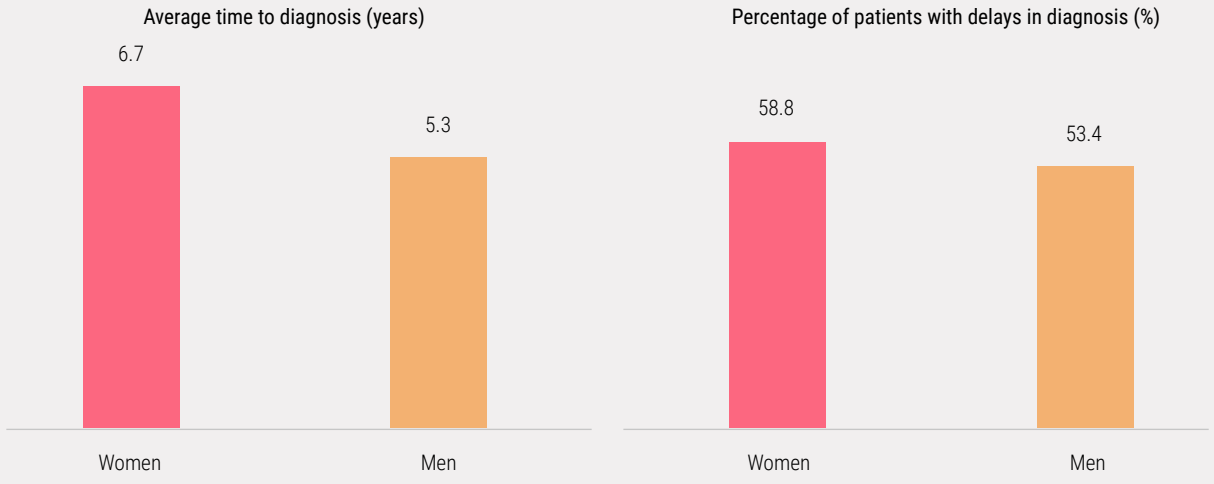
Source: *Kang (2023)*[53]

Gender inequality: relationship with delays in diagnosis

Late diagnosis has several consequences, including delays in the adoption of appropriate treatment and care. This often results in rapid disease progression, with serious implications for the quality of life, socio-economic status and mental health of those affected[54].

In Spain, women are 25% more likely to suffer a delay in diagnosis (>1 year) compared to men with RDs (OR: 1.25; 95%CI: 1.07-1.45, p=0.005). The mean waiting time for women to receive a diagnosis in RDs is 6.7 years compared to 5.6 years for men. 58.8% of women experience delays in their diagnosis, compared to 53.4% of men (Figure 19).

Figure 19. Time to diagnosis and delays in the diagnosis of RDs in Spain



Source: *Benito-Lozano (2022)*[55]

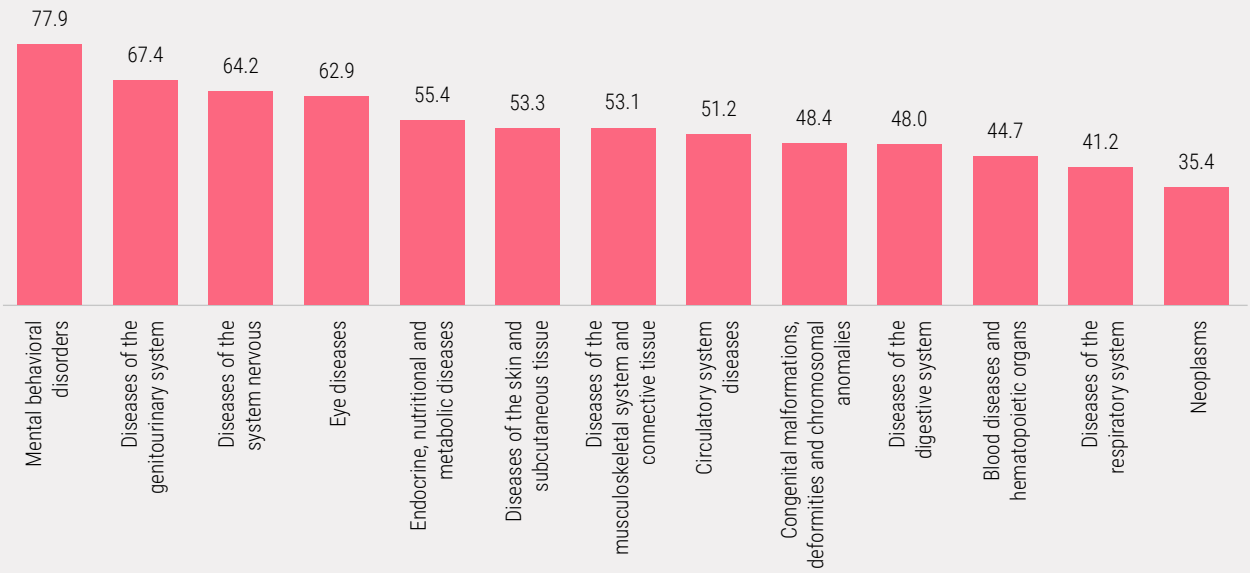
According to a report by the Rare Disease Alliance, there is a significant delay in medical care for French women compared to men when presenting with symptoms of RDs. In particular, the report shows that women are referred to hospitals and specialists later than men after the onset of symptoms, leading to a delay in diagnosis. According to the report's statistics, approximately 75% of men are referred to hospital less than three years after the onset of the first symptoms, while for women, approximately 75% are referred to hospital more than five years after the onset of symptoms[56].

The report also highlights that, on average, symptoms in men start to be treated before the diagnosis is confirmed, while in women, treatment usually starts after the diagnosis is confirmed. For men, about 50% start treatment for symptoms about a year after the onset of symptoms, and the diagnosis is confirmed after one and a half years. In contrast, for women, treatment for symptoms is not initiated in about 50% of cases until more than two years after the onset of the disease, which is almost nine months after the diagnosis has been established[56].

Disparities in diagnosis times depending on the type of RD

According to the same study by Benito-Lozano (2022) mentioned above, people who suffer the most from diagnostic delays are those with mental and behavioural disorders (77.9% of them suffer one year or more of diagnostic delay), with diseases of the genitourinary system (67.4%) and with diseases of the nervous system (64.2%). On the other hand, those with rare cancers (35.4%), diseases of the respiratory system (41.2%) and diseases of the blood and haematopoietic organs (44.7%) suffer the least (Figure 20).

Figure 20. Delays in diagnosis, by type of RD



Source: *Benito-Lozano (2022)*[55]

Racial inequalities: the case of sickle-cell disease

In the United States, sickle cell disease is an RD that predominantly affects the African American community, with 93% of the nearly 75,000 people hospitalised for the condition between 2016 and 2018 belonging to this community[57]. Furthermore, compared to whites, African Americans are three times more likely to experience crises related to the disease[57]. These crises are triggered when blood cells take the shape of a sickle and block tiny blood vessels that supply blood to specific organs, muscles and bones, causing pain that can range from mild to extremely severe, lasting from hours to days[58,59].

The approach to this condition varies according to the intensity and duration of pain experienced by the patient. In some cases, over-the-counter analgesics may be sufficient to relieve discomfort, while in other, more potent medications are required, which must be prescribed or administered by a healthcare professional. In acute pain situations, intravenous therapy may be necessary for the administration of fluids and highly effective medications such as morphine[58,59].

A meta-analysis conducted to assess inequalities in pain management in the United States revealed that the African American population faces a greater number and magnitude of disparities compared to any other group analysed. For example, African Americans were found to be 22% less likely than whites to receive "any type of analgesic" OR= 0.78, 95% CI= 0.68-0.89, p = 0.000), as well as 29% less likely than whites to receive opioid treatment for similar painful conditions (OR= 0.71, 95% CI= 0.63-0.80, p= 0.000)[60].

Inequalities in access to healthcare: LGBQT+ community

LGBQT+ people face discrimination in accessing health care. According to a 2017 survey in the United States, among respondents who identified as lesbian, gay, bisexual, queer and transgender (LGBQT+) and had seen a doctor or health care provider in the year prior to the survey[VII], 8% reported experiencing rejection by a doctor or other health care provider because of their actual or perceived sexual orientation. In addition, 6% indicated that they were denied medical care related to their sexual orientation, and 7% said that a doctor or other health care provider refused to recognise their family, including children or same-sex spouses or partners. In the case of transgender people, discrimination is even more alarming, with rejection rates reaching at least three times higher, ranging from 20% to 30%[61].

When multiple marginalised identities converge, such as self-identifying as part the LGBQT+ community, being female and living with a rare disease, experiences of marginalisation and inequality are intensified. A study with LGBQT+ women found that visibility of RD was positively correlated with RD stigma [r(27)=0.47, p=0.01]. In addition, greater visibility of sexual identity was associated with sexual stigma, [r(27)=0.35, p=0.06] and RD stigma was associated with sexual stigma [r(27)= 0.34, p=.07]. Common concerns raised by participants included stigma in healthcare, erasure of sexual identity, exclusion from the RDs and/or LGBQT+ community, and heteropatriarchal expectations and norms[62].

VII *In this study, the people did not have an RD.*

Referencias bibliográficas

1. Government of Spain. BOE-A-1986-10499. Law 14/1986 of 25 April 1986 on General Health.
2. Government of Spain. BOE-A-2003-10715. Law 16/2003, of 28 May, on the cohesion and quality of the National Health System..
3. Official State Gazette. BOE-A-2006-16212. Royal Decree 1030/2006, of 15 September, establishing the portfolio of common services of the National Health System and the procedure for updating it.
4. Government of Spain. BOE-A-2006-13554. Law 29/2006, of 26 July, on guarantees and rational use of medicines and health products.
5. Government of Spain. BOE-A-2006-21990. Law 39/2006, of 14 December, on the Promotion of Personal Autonomy and Care for Dependent Persons..
6. BOE-A-2011-15623. Law 33/2011, of 4 October, General Law on Public Health.
7. Government of Spain. BOE-A-2015-. Royal Legislative Decree 1/2015, of 24 July, approving the revised text of the Law on Guarantees and Rational Use of Medicines and Medical Devices..
8. Government of Spain. Congress of Deputies. Draft Bill amending various regulations to consolidate the equity, universality and cohesion of the National Health System. 2022.
9. Herrera MIM. Novedades en la Ley de Equidad Sanitaria. Available at: https://www.ineaf.es/tribuna/ley-de-equidad-sanitaria/.
10. Europa Press. Congress gives the green light to process the "Darias Law" to consolidate the equity, universality and cohesion of the SNS. Available at: https://www.infosalus.com/actualidad/noticia-congreso-da-luz-verde-tramitar-ley-darias-consolidar-equidad-universalidad-cohesion-sns-20220922145149.html.
11. Coiduras C. Los socios de Gobierno desbloquean la ILP de calidad sanitaria pero encallan la "Ley Darias". Available at: https://www.elplural.com/politica/socios-gobierno-desbloquean-ilp-calidad-sanitaria-encallan-ley-darias_307512102.
12. Salinas N. The private sector breathes in the face of the halt of the "Darias law" to shield public health. Available at: https://www.epe.es/es/sanidad/20230601/sector-privado-respira-paron-ley-sanidad-publica-88137434.
13. Spanish Association of Orphan and Ultra-Orphan Medicines Laboratories (AELMHU). Report on access to orphan drugs in Spain. 2023.
14. Spanish Association of Orphan and Ultra-Orphan Drug Laboratories (AELMHU). Annual report on access to orphan drugs in Spain. 2022.
15. IQVIA. EFPIA Patients W.A.I.T. Indicator 2022 Survey. 2023.
16. Government of Spain. Ministry of Health. Informe de evolución de la financiación y fijación de precios de los medicamentos huérfanos en el SNS 2016-2021). 2022.
17. Garc'a Parra B, Guiu JM, Modamio P, Martínez Yélamos A, Mariño Hernández E, Povedano M. Access to orphan drugs for the treatment of spinal muscular atrophy in Spain. Rev Neurol. 2022;75(09):261, doi: 10.33588/rn.7509.2022298.
18. Regional Government of Andalusia. Plan de Atención a Personas afectadas por Enfermedades Raras. [accessed 14 September 2023]. Available at: https://www.juntadeandalucia.es/organismos/saludyconsumo/areas/planificacion/planes-integrales/paginas/paper.html.
19. Consejer'a de Sanidad-Comunidad de Madrid. Plan for the Improvement of Health Care for People with Rare Diseases in the Community of Madrid. 2016-2020. 2016.
20. Community of Madrid. The Community of Madrid will update this summer its Rare Diseases Plan for the attention and care of these people. Available at: https://www.comunidad.madrid/noticias/2023/02/27/comunidad-madrid-actualizara-este-verano-su-plan-enfermedades-poco-frecuentes-atencion-cuidado-personas.
21. Regional Government of Extremadura. Annual report of the National Health System. 2004.
22. Regional Government of Extremadura. Integral Plan for Rare Diseases in Extremadura. 2010.
23. Regional Government of Extremadura. Integral Plan for Rare Diseases in Extremadura 2019-2023. Available at: https://www.juntaex.es/w/actuacion-plan-integral-de-enfermedades-raras-de-extremadura-pier-2019-2023.
24. Navarra Health Service. Health Strategy for Rare or Infrequent Diseases. 2017.

25. Regional Ministry of Health, Regional Ministry of Education, Youth and Sports, Regional Ministry of Family and Equal Opportunities of Murcia. Plan Integral de Enfermedades Raras de la Región de Murcia. Available at:https://www.carm.es/web/pagina?IDCONTENIDO=17298&IDTIPO=246&RASTRO=c890$m5859.

26. Department of Health - Galician Health Service. Galician Strategy on Rare Diseases. Available at: https://www.sergas.es/Asistencia-sanitaria/Estratexia-Galega-en-Enfermidades-Raras?idioma=es.

27. Government of the Canary Islands. Rare Diseases Strategy of the Canary Islands. Available at: https://www3.gobiernodecanarias.org/sanidad/scs/contenidoGenerico.jsp?idDocument=778a51b8-17bb-11ed-8a1a-1b6e6a9a9edd&idCarpeta=61e907e3-d473-11e9-9a19-e5198e027117.

28. Regional Government of Castilla y León. Plan Integral de Enfermedades Raras de Castilla y León (PIERCYL) 2023-2027. Available at: https://www.saludcastillayleon.es/institucion/es/piercyl.

29. Spanish Federation for Rare Diseases (FEDER). Map of Social and Health Policies for Rare Diseases. 2019.

30. Government of Spain. Ministry of Health. List of Reference Centres, Services and Units (CSUR) of the National Health System designated for the care or performance of the pathologies or procedures indicated. 2022.

31. Nguengang Wakap S, Lambert DM, Olry A, Rodwell C, Gueydan C, Lanneau V, et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum Genet. 2020;28(2):165-73, doi: 10.1038/s41431-019-0508-0.

32. Ministry of Health. Neonatal screening programme of the National Health System. Informe de evaluación. 2024, Available at: https://www.sanidad.gob.es/areas/promocionPrevencion/cribado/cribadoNeonatal/enfermedadesEndocrinoMetabolicas/docs/informes/InformeDeEvaluacionSICN_2021.pdf.

33. La Moncloa. Reference of the Council of Ministers of 16 April 2024. Available at: https://www.lamoncloa.gob.es/consejodemi- nistros/referencias/Paginas/2024/20240416-referencia-rueda-de-prensa-ministros.aspx.

34. Health portal of the Principality of Asturias. "Heel prick test" Programa de Cribado Neonatal de Enfermedades Endocrino-Metab—licas del Principado de Asturias (Neonatal Screening Programme for Endocrine-Metabolic Diseases of the Principality of Asturias). [accessed 18 January 2024]. Available at: https://www.astursalud.es/noticias?p_p_id=es_astursalud_liferay_portlet_AstursaludArticlesPortlet&p_p_lifecycle=0&p_p_state=normal&p_p_mode=view&_es_astursalud_liferay_portlet_AstursaludArticlesPortlet_article_id=53726&_es_astursalud_liferay_portlet_AstursaludArticlesPortlet_mvcRenderCommandName=%2Frender%2Farticle.

35. Cantabria Regional Ministry of Health. Heel prick test. Neonatal Screening Programme for Endocrine-Metabolic Diseases. [accessed 18 January 2024]. Available at: https://saludcantabria.es/index.php?page=metabolopias-hipotiroidismo-fenilcetonuria.

36. Indepf. Balearic Islands and Cantabria will extend their neonatal screening to 21 pathologies by 2024. INDEPF. 2023, Available: https://pocofrecuentes.org/islas-baleares-y-cantabria-ampliaran-su-cribado-neonatal-a-21-patologias-en-el-ano-2024/.

37. Order 167/2023, of 15 September, of the Regional Ministry of Health, regulating the diseases subject to neonatal screening and repealing Order 95/2022, of 20 May, on the prevention and control measures necessary to deal with the health crisis caused by COVID-19.

38. Community of Madrid. Neonatal screening. Community of Madrid. [accessed 18 January 2024]. Available at: https://www.comunidad.madrid/servicios/salud/cribado-neonatal.

39. Health Navarra. Screening programmes. Early Detection of Congenital Metabolopathies Programme. [accessed 18 January 2024]. Available at: https://www.navarra.es/home_es/Temas/Portal+de+la+Salud/Ciudadania/Nuevo+Modelo+asistencial/Programas+de+-cribado/PruebaTalon.htm.

40. Ministry of Finance and Public Function. Resolution of 22 December 2021, of the Mutualidad General de Funcionarios Civiles del Estado, publishing the Agreement signed with insurance companies to ensure access to health care in national territory for its beneficiaries during the years 2022, 2023 and 2024. BOE-A-2021-21337. vol. 2021.

41. Valencia incorporates three more diseases into neonatal screening. ConSalud.es. [accessed 18 January 2024]. Available at: https://www.consalud.es/autonomias/c-valenciana/valencia-incorpora-tres-enfermedades-mas-prueba-talon_121128_102.html.

42. DOG 235 of 13/12/2023 - DECREE 148/2023, of 23 November, regulating the Galician programme for the early detection of genetic, endocrine and metabolic diseases in the neonatal period and creating the programme's advisory committee.

43. Galicia X de. The Xunta expands the neonatal screening programme with three new diseases. Xunta de Galicia. [accessed 19 January 2024]. Available at: https://www.xunta.gal/notas-de-prensa/-/nova/86730/xunta-amplia-programa-cribado-neonatal-con-tres-nuevas-enfermedades.

44. Region of Murcia. The Region is one of the leading communities in the early detection of rare diseases with the neonatal screening programme. [accessed 18 January 2024]. Available at: https://www.carm.es/web/pagina?IDCONTENIDO=117251&IDTIPO=10&RASTRO=c$m122,70.

45. Charles River Associates. A landscape assessment of newborn screening (NBS) in Europe. 2021, Available at: https://www.sma-screening-alliance.org/wp-content/uploads/2022/12/CRA-LS-Insights-NBS-Policy.pdf.

46. Orphanet report series. Prevalence and incidence of rare diseases: Bibliographic data. 2021.

47. European Medicines Agency. Oxbryta| Voxelotor. [accessed 22 January 2024]. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/oxbryta.

48. CIMA: Medicines Information Centre. [accessed 19 January 2024]. Available at: https://cima.aemps.es/cima/publico/home.html.

49. Government of Spain. Ministry of Finance and Public Administration. Indicadores sobre gasto farmacéutico y sanitario. Available at: https://www.hacienda.gob.es/es-ES/CDI/Paginas/EstabilidadPresupuestaria/InformacionAAPPs/Indicadores-sobre-Gasto-Farmac%C3%A9utico-y-Sanitario.aspx.

50. INE. National Statistics Institute. Population figures and Demographic Censuses. Population projections. Available at: https://www.ine.es/dyngs/INEbase/es/operacion.htm?c=Estadistica_C&cid=1254736176953&menu=ultiDatos&idp=1254735572981.

51. Government of Spain. Ministry of Health. REEC - Spanish Register of Clinical Studies. Spanish Agency for Medicines and Health Products (AEMPS). [accessed 21 August 2023]. Available at: https://reec.aemps.es/reec/public/web.html.

52. Munro M, Cook AM, Bogart KR. An inductive qualitative content analysis of stigma experienced by people with rare diseases. Psychol Health. 2022;37(8):948-63, doi: 10.1080/08870446.2021.1912344.

53. Kang D, Choi S-E. Horizontal healthcare utilization inequity in patients with rare diseases in Korea. Int J Equity Health. 2023;22(1):93, doi: 10.1186/s12939-023-01903-9.

54. European Organisation for Rare Diseases. Gender inequalities and discrimination in rare diseases: a double threat to women's health. and wellbeing - EPHA. Https://Epha.Org/. Available at: https://epha.org/gender-inequalities-and-discrimination-in-rare-diseases-a-double-threat-to-womens-health-and-wellbeing/.

55. Benito-Lozano J, L—pez-Villalba B, Arias-Merino G, Posada de la Paz M, Alonso-Ferreira V. Diagnostic delay in rare diseases: data from the Spanish rare diseases patient registry. Orphanet J Rare Dis. 2022;17(1):418, doi: 10.1186/s13023-022-02530-3.

56. Alliance Maladies Rares. L'errance diagnostique dans les maladies rares. 2016.

57. Pokhrel A, Olayemi A, Ogbonda S, Nair K, Wang JC. Racial and ethnic differences in sickle cell disease within the United States: From demographics to outcomes. Eur J Haematol. 2023;110(5):554-63, doi: 10.1111/ejh.13936.

58. Michigan Medicine. Sickle Cell Crisis. Available at: https://www.uofmhealth.org/health-library/hw253529.

59. EveryLife Foundation for Rare Diseases. Rare Disease Racial Disparities. 2020, Available at: https://everylifefoundation.org/rare-advocates/rare-diversity-hub/disparities-in-public-health/.

60. Meghani SH, Byun E, Gallagher RM. Time to take stock: a meta-analysis and systematic review of analgesic treatment disparities for pain in the United States. Pain Med Malden Mass. 2012;13(2):150-74, doi: 10.1111/j.1526-4637.2011.01310.x.

61. Center for American Progress. Discrimination Prevents LGBTQ People From Accessing Health Care. 2018, Available at: https://www.americanprogress.org/article/discrimination-prevents-lgbtq-people-accessing-health-care/.

62. Munro M, Voight DM, Bryson BA, Bogart KR. Enacted Stigma Experiences and Identity Noticeability of LGBQ+ Women with Rare Diseases. J Homosex. 2023;70(11):2348-73, doi: 10.1080/00918369.2022.2059971.

Chapter 3

Orphan drugs regulatory process

Laws, regulations and policies are crucial elements in promoting public welfare, security, justice, competition and development. In the field of rare diseases (RDs), the regulatory framework plays an even more crucial role in promoting research and treatment development, access to adequate and equitable medical care and treatment, protecting patients' rights, encouraging the development and implementation of new and innovative treatments for rare diseases and raising public awareness.

Due to the different characteristics of RDs, the development and research of therapies to prevent and treat them can be challenging from a methodological, evaluative and commercial point of view. To address this issue, several countries and supranational organisations have adopted specific regulations to promote the development of and access to therapies for RD.

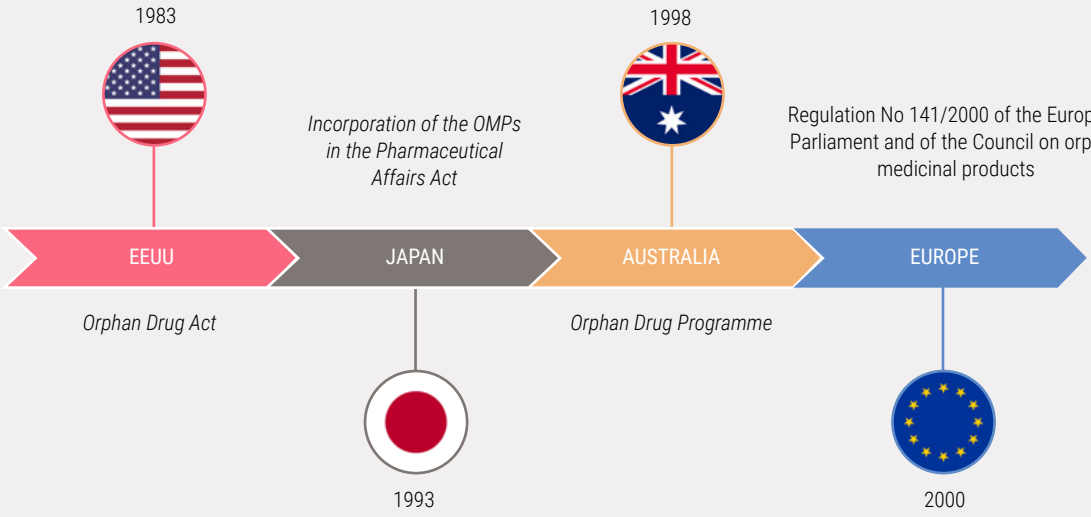
This chapter outlines the importance of establishing an appropriate regulatory framework for OMPs and provides an overview of the regulatory and normative background. This is followed by an analysis of the EU legislation, as well as the main laws, guidelines, evaluation and funding mechanisms affecting OMPs in some European countries. Finally, the current regulatory framework in Spain is explained, including some regional strategies on rare diseases, and some lines for the future are presented.

3.1. Importance and background

For more than three decades, there has been a growing need in different countries to regulate and legislate some aspects of rare diseases and medicines targeted towards them. This idea born out of the significant burden disease often faced by both family members and patients suffering from these illnesses, coupled with the lack of treatments, due to low commercial interest from the pharmaceutical industry, as well as certain complications in research[1]. Legislation can also help to promote equity in medical care by helping to ensure equal access without discrimination based on the rarity of their disease or the region in which they live.

In this context, the US was the first country to develop a specific law, the Orphan Drug Act of 1983[2]. This law granted a series of incentives, such as federal grants and contracts for clinical trials, tax discounts of 50% on the costs of clinical trials and exclusive marketing rights for 7 years for pathologies affecting less than 200,000 inhabitants, as opposed to the 5 years of protection for other drugs[1-3]. It also allowed other benefits, such as fee waivers when applying for drug approval from the Federal Drug Administration (FDA). This legislation has been considered a success in terms of access[4], with an increase from 58 approvals of OMPs in the period 1967-1983[5] to more than 600 from 1983 to 2020[6]. Following in the footsteps of the US, other countries such as Japan[7] or Australia[8], or in our context, the EU[9], have adopted similar specific legislation (Figure 1).

Figure 1. Specific legislation on rare diseases in different countries



Note: ***OMPs:*** *Orphan medical products.*

Source: *own elaboration based on US Senate (1983)[2], Nagaraja (2020)[7], Therapeutic Goods Administration (TGA) (2020) and European Council (2000)[9]*

3.2. Regulatory framework in Europe

Current EU pharmaceutical legislation includes both general and specific legislation. The first specific legislation for OMPs came into force in 2000, based on the European Parliament and Council Regulation 141/2000 on OMPs. This regulation defined what is considered a rare disease in the EU and approved a series of incentives for medicinal products designated as orphan medicinal products[9]. Thus, OMPs must be centrally authorised by the EMA, as well as therapies targeting certain diseases (HIV, cancer, diabetes or degenerative, autoimmune or viral pathologies) or derived from biotechnological processes or genetic modification. The rest of the of non-orphan medicinal products for the treatment of rare diseases can apply for marketing authorisation through any type of procedure (national, decentralised, mutual recognition or centralised)[11].

In order to obtain marketing authorisation as an orphan medicinal product by the EMA, drugs must have been previously designated as such by the European Commission, following a recommendation by the EMA's Committee for Orphan Medicinal Products (COMP). For this designation, criteria such as disease prevalence, severity, unmet need, potential economic return and potential benefit over therapeutic alternatives are taken into account[12].

The aim of the regulation was on one hand to ensure research and development (R&D) in OMPs by introducing a greater number of designated orphan drugs on the market (availability) and, on the other hand, to assure patients that the efficacy, safety and quality of these treatments is equivalent to that of any other (accessibility).

To be eligible for benefits, the therapy must meet the following criteria[13]:

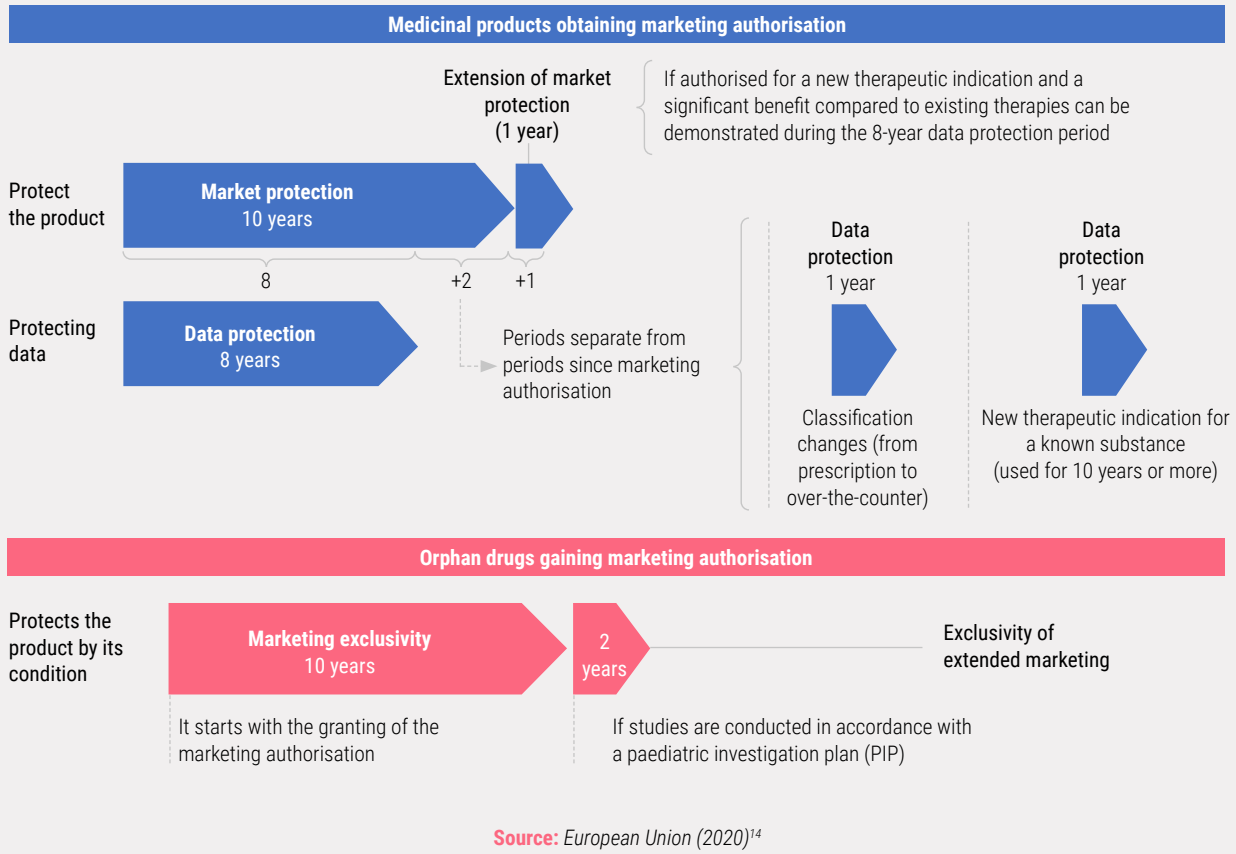
- Target a disease whose prevalence in the EU does not exceed 5 per 10,000 population, or where commercialisation is unlikely to generate sufficient returns to justify the investment required for its development.
- Intended for the treatment, prevention or diagnosis of a life-threatening or chronically debilitating disease.
- There is no satisfactory method of diagnosis, prevention or treatment of the condition in question or, if such a method exists, the medicinal product under evaluation is of significant additional benefit.

The European regulation establishes a two-stage procedure:

- First, a company can apply for a product to be granted an "orphan designation" at any stage of development, which may allow it to obtain R&D funding and for the product to receive specific support from the EMA before marketing authorisation is granted by the Agency. Orphan designation" is made per indication of the medicinal product.
- Once development is complete, the product can, as a second step, benefit from an EU-wide marketing authorisation, with a period of market exclusivity of 10 years (or 12 years for paediatric use). If after 5 years the product still does not meet the criteria for orphan designation, the period of market exclusivity can be shortened to 6 years.

The difference in innovation incentives for different medicines in Europe can be seen in Figure 2.

Figure 2. Comparison of incentives for OMPs and prevalent diseases



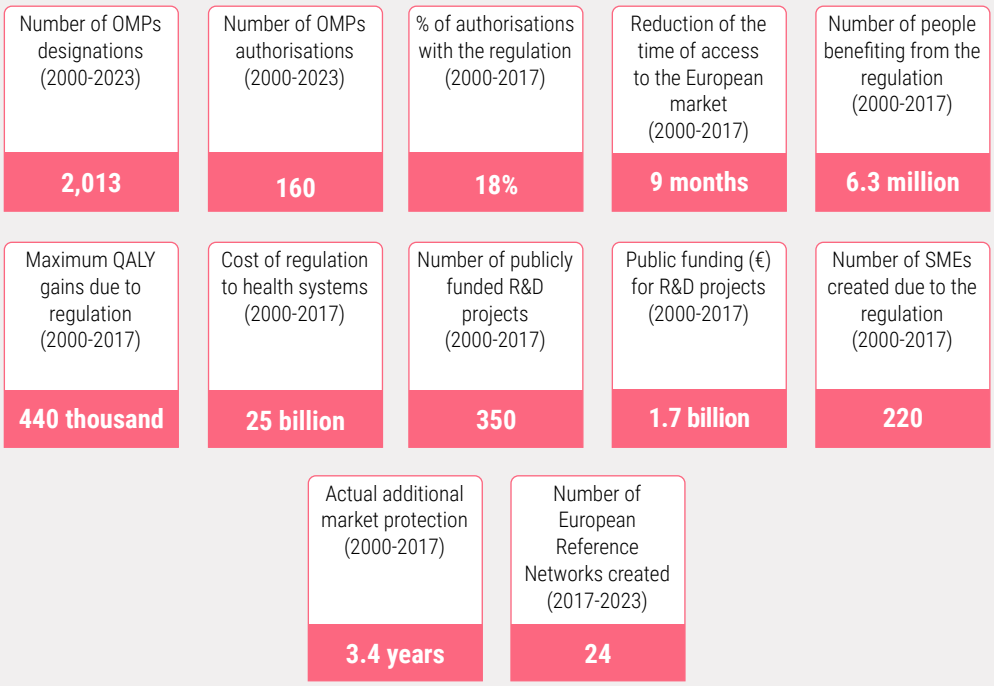
Source: *European Union (2020)*[14]

To incentivise the development of designated orphan therapies, the European Commission also established the following advantages[15]:

- Specific scientific advice, at a reduced cost, to help companies decide how best to provide robust evidence on the quality, efficacy and safety of the drug.
- Centralised marketing assessment, allowing a single marketing decision for all EU Member States.
- Additional administrative assistance for SMEs.
- Reduced marketing application fees, pre-approval inspections, post-approval requests for changes to marketing authorisations and reduced annual fees.
- Additional R&D funding under Horizon 2020 and E-Rare.

The regulation about OMPs has had a notable impact on the number of designations and approvals, as well as on other aspects such as the number of research projects, the number of companies created or the number of people benefiting from it. The European Commission itself published a document in 2020 quantifying this impact in Europe (Figure 3).

Figure 3. Impact of the European Regulation for ODs



Notes: ***QALYs:*** *Quality Adjusted Life Years;* ***R&D:*** *research and development;* ***OMPs:*** *orphan medicinal product;* ***SMEs:*** *small and medium-sized enterprises.*

Sources: *European Commission (2020)*[16]*, EMA (2020)*[17,18] *and European Union (2020)*[19]

Furthermore, this assessment indicates that the legislation stimulated the development of 21 OMPs in the period from 2000 to 2017, having a relative impact of 20%. This assessment contrasts with that of other authors who have also analysed the impact of European regulations. Some of them indicate that more than half of the orphan medicines developed between 2000 and 2017 (74 out of 142 developed) would not have been economically viable without such legislation[20].

The difference between the two assessments stems from the fact that the analysis published by the Commission assumed that, in the absence of the legislation, the number of orphans would have grown at the same rate as the number of non-orphans. They then observed that OMPs were approved at a faster rate during the period 2012-2017 and, finally, attributed the difference between approved and expected OMPs to the legislation, given the trends in the OMPs market. The other authors point out that this assumption is not correct, as the OMPs legislation was introduced precisely because OMPs were not developing at a rate even close to that of non-orphan drugs, which they did take into account[20].

➜ European pharmaceutical strategy

Over time, the European Commission undertook a review of the pharmaceutical policies, which was formalised with the publication of the new European Pharmaceutical Strategy, adopted in 2020, with the aim of establishing forward-looking regulation and supporting the pharmaceutical industry in promoting research and technologies that reach patients to meet their therapeutic needs, while addressing market failures[21]. In this sense, the European Strategy seeks to prioritise unmet medical needs, promoting R&D related to disease prevention and treatment, facilitate access to safe, effective and high-quality medicines, and become more patient-centred. Specifically, this strategy initiated a reflection process on how to adapt the incentive provided by the EU pharmaceuticals framework to stimulate innovation in areas where there are unmet medical needs, such as RDs[22].

This reflection has led to the proposal for a revision of the European pharmaceutical legislation, repealing Regulation 141/2000 and merging the current regulations on OMPs and paediatric medicinal products, in order to promote greater coherence and simplification[23]. Medicinal products for RDs will continue to be subject to the same rules as any other medicinal product with regard to their quality, safety and efficacy and in terms of marketing authorisation procedures, pharmacovigilance and quality requirements. However, specific requirements will also continue to apply, to support their development. These requirements, currently laid down in separate legislative acts, will be integrated into the Regulation and the Directive, to ensure clarity and consistency.

Based on the evaluation of the legislation on medicines for rare diseases and children published by the European Commission in 2020[24], the following shortcomings were identified[25]:

- Rare disease patients and children medical needs are not sufficiently met.
- The affordability of medicines is a growing challenge for health systems.
- Patients have unequal access to medicines in the EU.
- The regulatory system does not take sufficiently into account the innovation and, in some cases, creates an unnecessary administrative burden.

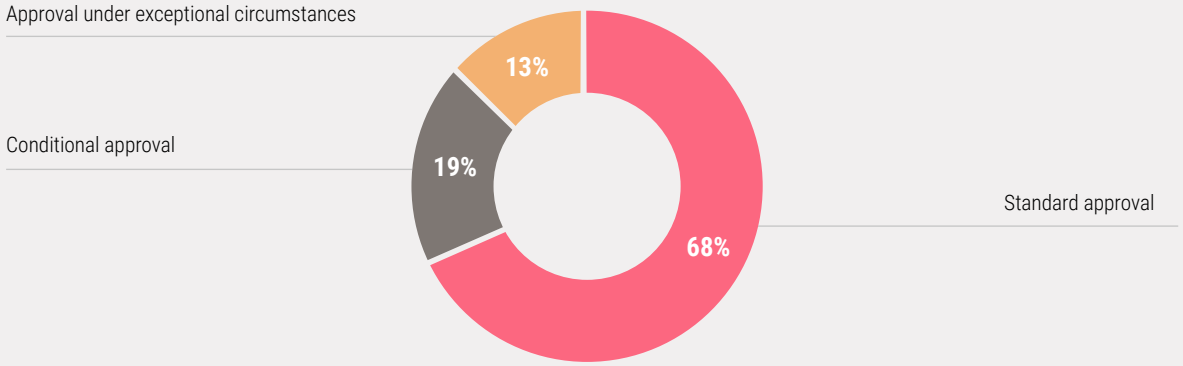
To overcome these points, it is suggested that the period of market exclusivity for OMPs should have a variable duration of ten, nine and five years, based on the type of orphan medicinal product in question. Be it for a major unmet medical need (or UMN), new active substances and well-established use applications, respectively. An additional one-year extension of market exclusivity may also be granted on the basis of patient accessibility in all relevant Member States, but onlyfor UMN products and for new active substances[25].

OMPs EMA approvals characteristics

For marketing approval by the EMA, OMPs are assessed following the same process as others[12], although the EMA offers some flexibility, through conditional approval and approval under exceptional circumstances, used to approve drugs early and on the basis of less evidence. Due to the characteristics of RDs, both conditional approvals and approvals under exceptional circumstances are used more intensively for the approval of OMPs than for the approval of medicines for prevalent diseases.

Currently, 143 OMPs are authorised by the EMA, of which 97 (68%) have followed the standard approval procedure, 27 (19%) have been approved through conditional approval and 19 (13%) through exceptional circumstances (Figure 4).

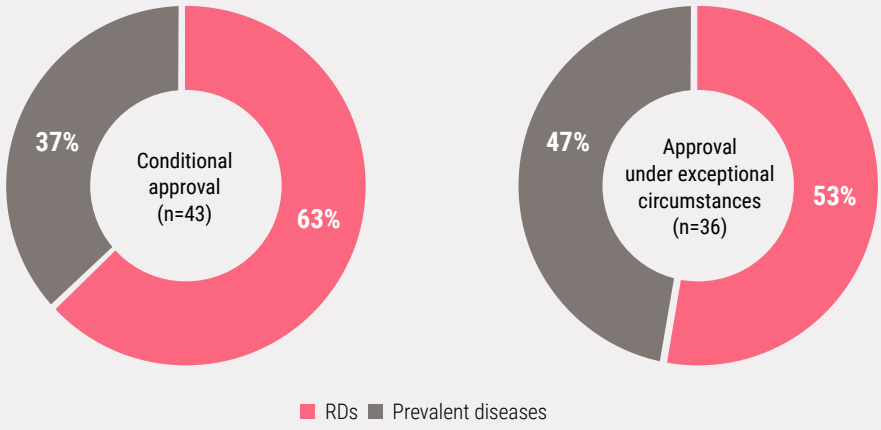
Figure 4. Type of procedure applied to the 2006-2023 OMPs



Source: *own elaboration based on EMA[18]*

Sixty-three percent of the 43 conditional approvals have been for RDs, while the remaining were approved for other diseases. More than half of the drug approvals under exceptional circumstances were for OMPs (Figure 5).

Figure 5. Applicability of EMA procedures, 2006-2023

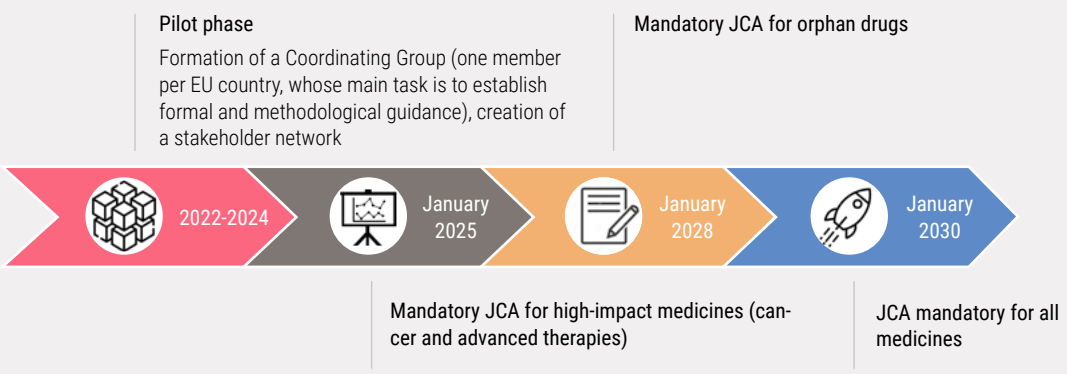


➜ Joint clinical assessment

Another relevant element is the Regulation 2021/2282 on Health Technology Assessment, which the European Commission adopted in 2021, to ensure the proper functioning of the internal market for medicinal products, medical devices and in vitro diagnostic products[26]. The Regulation establishes a framework to support Member States' cooperation and the necessary arrangements to promote the Joint Clinical Assessment (JCA) of health technologies at European level.

Although the regulation entered into force in 2021, effective implementation will not start until 2025, starting with oncology medicines containing new active substances and advanced therapies (i.e. gene therapy, cell therapy and tissue engineered products), OMPs will be involved in 2028 and all other medicines from 2030 onwards[27].

Figure 6. Planning the joint European clinical assessment



Note: *JCA: Joint Clinical Assessment.*

Source: *adapted from the Official Journal of the European Union*[28]

The Coordination Group will be responsible for conducting joint assessments of medicinal products, with the aim of replacing the parallel assessments of clinical data conducted by multiple country-specific assessment bodies with a single harmonised assessment. However, these assessments will be non-binding, so that the conclusions on the efficacy and safety of medicinal products made by each member country will not be affected by the JCA. Likewise, the findings of the JCA will not affect national pricing and reimbursement decisions[26,29].

Specifically, the Coordination Group will take into account the specificities of the health technology addressed by the assessment, in particular OMPs, vaccines and advanced therapies[26]. To ensure inclusiveness and transparency in the joint work, the Coordination Group will consult with a broad spectrum of stakeholders, including patient organisations, health professionals, clinical and academic societies, health technology developers, consumers and other non-governmental health organisations. In addition, a stakeholder network will be established to facilitate dialogue with the Coordination Group, and external experts with relevant expertise will contribute to the process.

The joint assessment process can be divided into 4 phases[30]:

1. The scoping phase, covering the development and validation of the PICO scheme (patient population, intervention, comparator(s), and health outcomes)[26]
2. Development phase of the JCA dossier
3. JCA Dossier Assignment Phase
4. The publication of the final report of the JCA

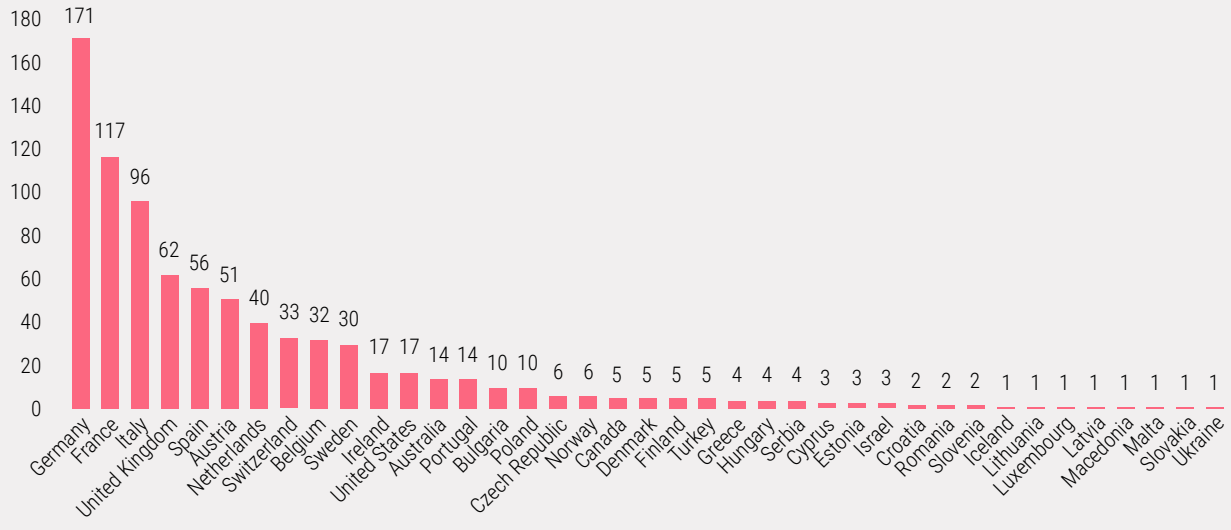
➜ European networks and registers of RDs

Research networks and registries are essential tools for addressing the challenges associated with RDs by enabling the collection of critical data, boosting the understanding and treatment of these diseases. The benefits of RDs registries include the ability to estimate effectiveness in a variety of different clinical settings, comparability with multiple therapeutic alternatives, estimation of risks and benefits, clinical outcomes in a diverse population, and the distribution of patients observed in clinical practice[31]. In general, registries are used for prospective, cohort studies of patients presenting with a particular pathology or receiving a particular treatment. These registries can be used for many purposes, such as improving knowledge of the natural history of the disease, and monitoring or assessing the safety of a drug[31].

At the European level, there is the European Platform on Rare Disease Registration, whose main objective is to address the huge fragmentation of rare disease patient data contained in hundreds of registries across Europe. The Platform makes data from rare disease registries easily searchable and findable, thereby increasing the visibility of each registry, maximising the value of the information and enabling widespread use and re-use of the data. The European Rare Disease Registry Infrastructure (ERDRI) supports existing registries as well as the creation of new ones and allows searching and finding rare disease registry data through a European directory of registries (ERDRI.dor), a central metadata repository (ERDRI.mdr), a pseudonymisation tool (ERDRI.spider) and a search agent (ERDRI.sebro)[32]. The EU RDs Platform sets EU-wide standards for the collection and exchange of data and provides training on the use of the tools and services offered[33].

In addtition, according to Orphanet, as of April 2023, there were a total of 827 registries for more than 985 RDs in Europe, of which 550 (67%) were at the national level, 91 (11%) at the regional level, 91 (11%) at the European level and 95 (12%) at the global level. In Spain, a total of 56 registries have been identified, which places us in fifth position, after Germany (171), France (117), Italy (96) and the United Kingdom (56) (Figure 7)[33].

Figure 7. Number of RDs registries and databases collected by Orphanet, by country



Source: *Orphanet (2023)*[33]

Furthermore, in 2014, the European Commission adopted the Directive 2011/24/EU related to patients' rights in cross-border healthcare, highlighting the importance of creation of European Reference Networks (ERNs) and setting the criteria for the creation and evaluation of such networks, in order to facilitate the exchange of information and experience between them[34]. ERNs aim to address rare or complex diseases or conditions, which require highly specialised treatment and a concentration of expertise and resources. These networks help to provide affordable, high-quality and cost-effective healthcare to patients whose conditions require a particular concentration of resources or expertise[35]. This system began its activity in 2017, encompassing 24 thematic networks (17 of which have a Spanish contribution) and with the participation of 300 hospitals and 900 healthcare centres from 26 countries, allowing healthcare professionals access to consolidated theoretical and practical knowledge on RDs, which would otherwise be fragmented in different countries[19].

➜ Regulatory process in other neighbouring countries

In addition to the legislation and strategies established at the European level, various countries around us have adopted specific regulations on RDs, either with different evaluation processes, relaxed conditions regarding the effectiveness of the medicines to be evaluated or faster market entry.

England

In England, the marketing of OMPs is dependent on the marketing authorisation granted by the Medicines and Healthcare products Regulatory Agency, which is the competent authority regulating marketing authorisations in the country and responsible for reviewing applications for orphan designation[36]. Unlike the EU procedure, it is not possible to obtain an advanced orphan designation[37]. For a medicinal product to be designated as an orphan medicinal product, the following conditions must be met[36]:

- It must be intended for the treatment, prevention or diagnosis of a life-threatening or chronically debilitating disease.
- The prevalence of the disease in Great Britain must be no more than 5 per 10,000 population, or the marketing of the drug must be unlikely to generate sufficient benefits to justify the investment required for its development.
- No satisfactory method of diagnosis, prevention or treatment of the disease in question currently exist in Great Britain or, if such a method exists, the medicinal product must be of significant benefit to persons affected by the disease.

If orphan status is granted, the medicine will benefit from up to 10 years of market exclusivity. This exclusivity can be reduced to 6 years if requested by the UK authorities. They also offer full or partial reimbursement of marketing authorisation fees to encourage the development of medicines in orphan diseases, as well as a waiver of scientific advice fees for UK-based SMEs[36].

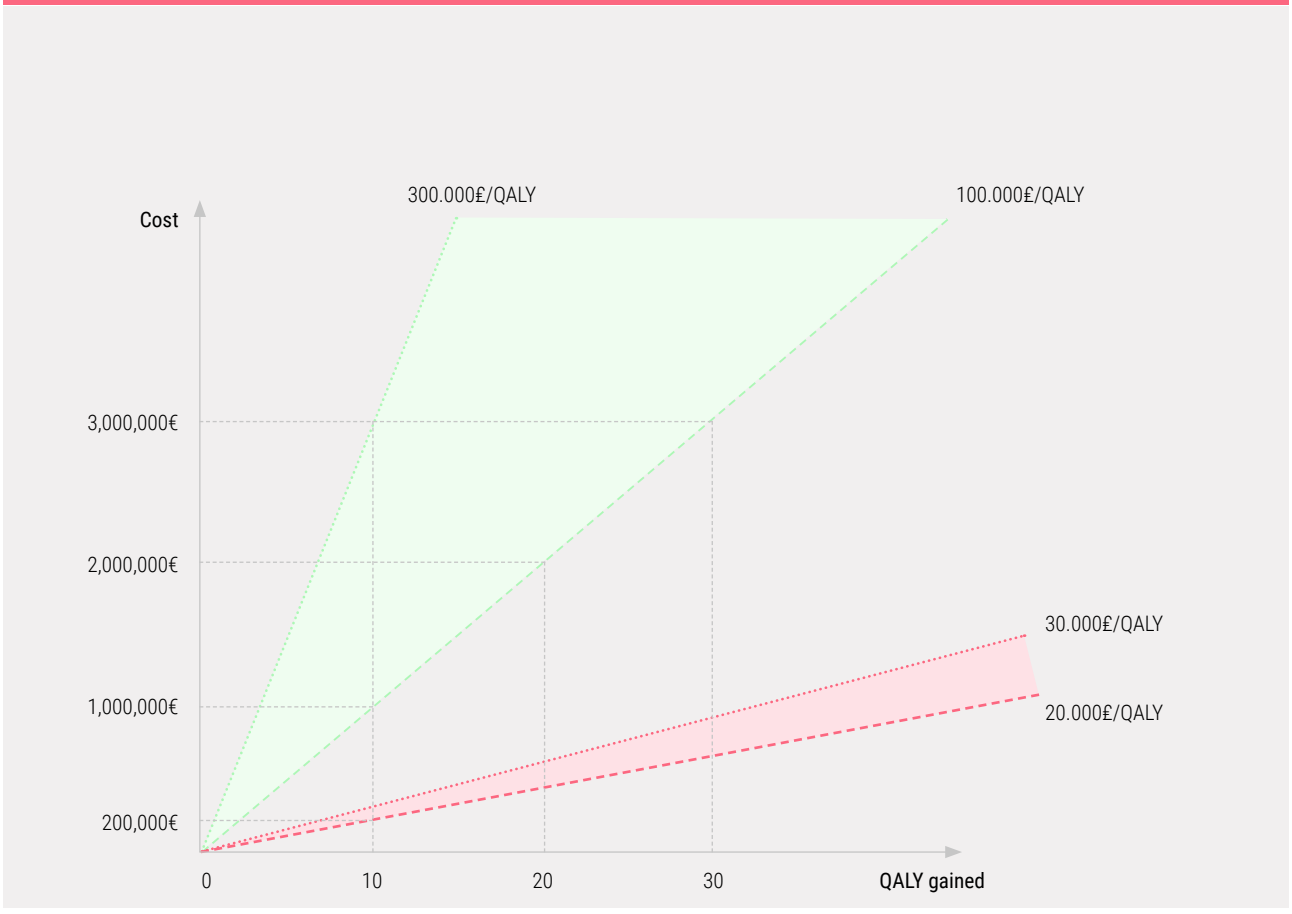
When assessing specialised technologies, the UK assessment agency (National Institute for Health and Care Excellence or NICE) may deviate from its standard methodology and use a different assessment method to that used for other medicines, such as the highly specialised technology assessment, which is available for medicines indicated for rare and very specific conditions. This assessment is only available for medicines that meet the following conditions[38]:

- The target patient group is either clinically distinct or small enough to be treated in a few English NHS centres.
- The disease is chronic and highly disabling.
- The drug has the potential to be used throughout the patient's life.

The decision-making criteria are not only based on the criteria of effectiveness and efficiency usually considered in the standard evaluation process, but on other additional criteria, such as the morbidity of the disease, the nature of the available treatment options, and the overall magnitude of the health benefits for patients, among others[39].

NICE recommends drug funding based on its cost effectiveness ratio which is the difference in cost between the new drug and its available alternative, divided by the difference in clinical effectiveness between the two drugs[40]. The cost-effectiveness threshold consists of setting a maximum cost-effectiveness ratio of willingness to pay, i.e. beyond this value the funder is not willing to pay that amount. In this sense, when making a cost-effectiveness decision, NICE considers a standard threshold of approximately £20,000-30,000 (€24,000-36,000) per Quality Adjusted Life Year (QALY) gained to recommend funding for any therapy. For highly specialised technologies, it allows the upper limit of the threshold to be extended depending on the impact of the therapy on the patient's life, ranging from £100,000 (approx. €120,000) per QALY per year for treatments that provide less than 10 additional QALYs to the patient, to a maximum of £300,000 for treatments that provide more than 30 additional QALYs over a lifetime (Figure 8)[41–43].

Figure 8. Cost-effectiveness thresholds for OMPs and prevalent diseases in England



Note: ***green area:*** *range of cost-effectiveness thresholds for OMPs;* ***red area:*** *range of cost-effectiveness thresholds for prevalent diseases.*

Source: *own elaboration*

Scotland

The Scottish Medicines Consortium (SMC) has an early access mechanism for so-called "ultra-rare" diseases. For a medicine to be approved through this process, it must meet the following conditions[44]:

- Prevalence less than 1/50,000 people in Scotland
- Orphan marketing authorisation by the UK regulator
- Be targeted at a chronic and severely disabling disease
- Targeting a disease that requires highly specialised treatment

For the assessment of these types of therapies, the SMC allows companies to submit preliminary information after they have obtained marketing authorisation as an OMP. Once the information is received, the SMC conducts an initial assessment of the therapy's clinical and economic efficacy. The SMC uses a broad framework to assess OMPs, taking into account the following criteria[44]:

- Nature of the disease
- Impact of the medicine
- Value for money
- Impact of the technology beyond direct health benefits
- Costs for the NHS and social services

This authorisation is valid for three years during which time additional data will be collected from actual clinical practice in Scotland. After that period, the company must submit the evidence shown by the medicine for the therapy to be re-evaluated for inclusion in routine use in the NHS [44].

As in England, Scotland uses different cost-effectiveness thresholds, called modifiers, to make funding decisions. Some of these modifiers are applied if there are no other therapeutic options of proven benefit for the condition in question, or if there is evidence that a subgroup of patients may derive a specific or additional benefit and that the drug in question can be targeted to this subgroup in practice[45].

France

In 2021, France reformed its temporary authorisation to use (ATU) system to a new early access system, with the aim of simplifying and harmonising procedures, ensuring immediate access and care for patients, while guaranteeing the financial sustainability of the system. This reform put in place two new mechanisms for access and health insurance coverage that can be applied to OMPs[46]:

- "Early Access" which targets medicines that address an unmet therapeutic need, which may be innovative and for which the laboratory commits to submit a marketing or a request for reimbursement.
- "Compassionate access" which targets medicines that are not necessarily innovative, which are not initially intended to obtain a marketing authorisation, but which respond satisfactorily to an unmet therapeutic need.

The new "early access" system is mainly used for innovative medicines and applications for this route must be made to the High Authority for Health (Haute Autorité de Santé or HAS), which has three months to communicate its decision and the manufacturer must also agree to make the product available within two months of authorisation. One of the advantages of this system is that the clinical data for this type of assessment must be collected through a standardised process, so it is possible for HAS to take these data into account in the clinical assessment which may lead to a faster review of the medicine assessment and a quicker time to reimbursement[47].

Another novel aspect included in this reform is the introduction of the presumption of innovation of medicines with respect to their comparator. Furthermore, the laboratory can set a free price for these products and if the final negotiated price is lower than the price set during early access, manufacturers will have to refund the difference[47].

Therapies seeking access through compassionate access must address the lack of commercial clinical research i.e. no pharmaceutical laboratory conducts clinical research for commercial purposes. In this case, the laboratory must follow an established clinical protocol and collect data for the required period. The price and reimbursement of the medicine in this type of access depends on whether the product is reimbursed in another indication. If this is the case, the price and reimbursement of the medicine will be the same as the price and reimbursement of the medicine in the previously reimbursed indication. However, if the product is not reimbursed in another indication, the laboratory is free to set the price[47].

Germany

Germany works differently from other countries. Companies can introduce a medicine at any initial price and it is fully reimbursed by the German insurance schemes for the first 7 months[48] (until recently, it was for the first 12 months[49]). Reimbursement prices and financing arrangements are then negotiated, with the results of the evaluation playing a key role. This assessment ranks the additional benefit of a drug relative to its comparator on a 6-level scale (Table1)[50]:

Table 1. Scale of measurement of benefit in Germany

Type of benefit	Definition
Exceptional additional benefit	Sustained and substantial improvement in benefit. This is a highly relevant benefit that has not previously been achieved with the appropriate comparator, and can be identified by recovery from the disease, a measurable increase in life expectancy, long-term relief of severe symptoms, or a highly relevant avoidance of serious side effects.
Significant additional benefit	Significant improvement in benefit. It is relevant to the therapy, was not previously achieved with the appropriate comparator, and can be identified in particular by attenuation of severe symptoms, a moderate prolongation of life, a patient-noticeable "alleviation" of the disease, or the therapy's avoidance of important serious or other side effects.
Minor additional benefit	Moderate or mild improvement in benefit. It is relevant to the therapy, was not previously achieved with appropriate comparators, and in particular may be identified as a reduction in non-severe symptoms of the disease or that the new therapy avoids certain side effects.
Unquantified additional benefit	When the available scientific data do not allow for quantification.
No additional benefit	No additional benefit has been demonstrated.
Minor benefit	When the benefit of the tested medicine is less than that of the comparator.

Source: *own elaboration based on OECD (2018)*[50]

Germany does not have a differentiated assessment process, but in the case of OMPs, the German assessment agency (G-BA) assumes an additional therapeutic benefit, taking into account the data provided by the pharmaceutical company for marketing authorisation, without considering any comparator, as long as the expenditure for compulsory insurance does not exceed 50 million of euros per year (in the latest reform proposed by the German government, this figure is proposed to be reduced to 20 million euros)[51]. Manufacturers are exempted from submitting data to support this benefit, but the G-BA assesses the magnitude of the benefit to create a basis for price negotiation. If annual sales exceed this threshold, the pharmaceutical company is obliged to submit data on the additional therapeutic benefit and both the assessment and price negotiation of the OMP follows the same process as for medicines for prevalent diseases.

Italy

The transalpine country has several measures in place to favour the entry of orphan medicinal products into the country. First of all, in order to accelerate the availability of orphan medicinal products in the country, the Balduzzi Law (Law 189/2012) established that the pharmaceutical company holding a marketing authorisation for an orphan medicinal product may submit an application for pricing and reimbursement to the Italian Medicines Agency (AIFA) after the positive opinion of the Committee for Medicinal Products for Human Use (CHMP), i.e. before the European Commission issues the marketing authorisation at European level. In turn, this law establishes that AIFA will assess as a priority, for the purposes of classification and reimbursement by the National Service, orphan medicinal products and medicinal products of exceptional therapeutic importance for which an application has been submitted. In this case, the assessment period is reduced to 100 days[52].

In Italy, a patient suffering from a rare disease can have access to an orphan medicinal product through various legislative instruments. The centralised authorisation procedure through the EMA represents the main access rule. However, in the absence of a marketing authorisation for an orphan medicinal product indicated for a rare disease, a patient suffering from a rare disease can access the medicinal product through one of the following procedures[52,53]:

- Early access based on patient cohorts and off-label use. Law 648/1996 allows the use of a medicine at national level for diseases for which there are no valid alternatives (or where there are problems of access) or which are less expensive than available therapies (economic problems). Any interested party (patient associations, scientific societies, health care organisations, doctors, etc.), with the exception of industry, can apply. The Italian regions should send a quarterly report to AIFA on the clinical and economic impact of the medicines included in the list, although in reality the data are not systematically collected and are not publicly available.

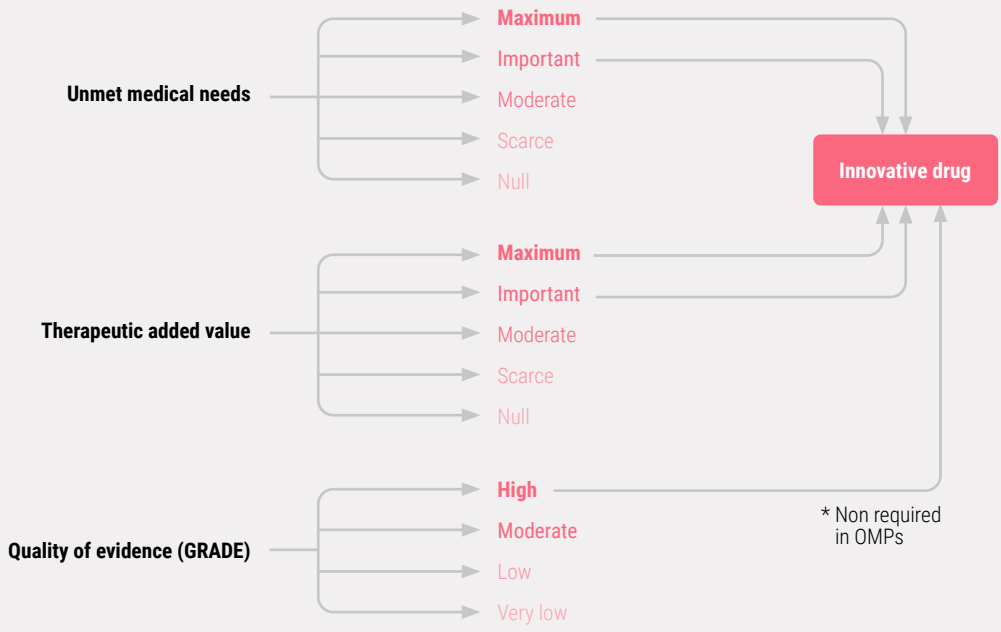
- Prescription of the medicine to the patient on an individual basis and not in cohorts (regulated by Law 94/1998).

- AIFA 5% Fund: Regulated by Law 326/2003, the fund covers orphan drugs and drugs in development for rare and serious diseases, not yet approved. The fund is managed by AIFA and is financed by the 5% tax paid by all pharmaceutical companies on commercial expenses. In 2021, this fund handled 1,805 requests and accounted for a total expenditure of 81.2 million euros.

- Compassionate use. Regulated Ministerial Decree 5/8/2013, compassionate use covers medicines/indications for which there are no valid therapeutic alternatives. These medicines/indications may be in clinical development or approved, but not yet covered by the Italian National Health Service. Medicines used in compassionate use programmes are fully covered by pharmaceutical companies.

On the other hand, when performing the medicine clinical evaluation, the Italian authorities use an algorithm to measure the "innovation" of the medicine based on the unmet needs of the pathology, the added therapeutic value of the medicine compared to its comparators, and the quality of the evidence demonstrated by the medicine to be evaluated. In the case of OMPs, the Scientific Technical Committee takes into account the difficulty of conducting clinical trials in these pathologies and is not flexible with the quality of evidence required when evaluating these therapies (Figure 9)[54].

Figure 9. Criteria and levels of the innovation algorithm in Italy



Note: ***OMPs****: Orphan medicinal products*

Source: *Own elaboration based on AIFA*[54]

3.3. Regulatory framework for ODs in Spain

In Spain, there is no specific regulation for orphan medicinal products, although some progress has been made. Firstly, as mentioned in the previous chapter, article 92 of RD-legislative 1/2015, of 24 July, which approves the revised text of the Law on Guarantees and Rational Use of Medicines and Medical Devices, establishes that the inclusion of medicines in the National Health System funding is made possible by taking into account different criteria, such as the specific needs of certain groups including patients with RDs[55].

On the other hand, access to medicines outside the conventional price and reimbursement procedures is determined by RD 1015/2009, which includes three types of special uses: compassionate use, off-label and foreign medicines.

Compassionate use of medicines encompasses the use of investigational medicines that have not yet been authorised in patients with chronic or severely debilitating life-threatening diseases that cannot be successfully treated with an authorised medicine. There are two procedures by which access to investigational medicinal products for compassionate use can be requested[56]:

a) Individualised access authorisation. Through this procedure, the hospital, after approval by its management department, requests permission from the Spanish Agency for Medicines and Health Products (AEMPS) to use the medicine for a specific patient or a group of patients.

b) Temporary authorisations for use. The AEMPS may issue a temporary authorisation decision for the use of investigational medicinal products outside a clinical trial if it foresees their use in a significant group of patients. This eliminates the need to request authorisation for use on an individual basis for each patient or groups of patients.

This type of authorisation can only be granted for medicinal products in advanced stages of clinical research (and with the intention to apply for a marketing authorisation) or those that have already applied for a marketing authorisation[56].

Off-label or off-label uses "shall be exceptional in nature and in situations where there is a lack of authorised therapeutic alternatives for a given patient, respecting, where appropriate, the restrictions that have been established linked to the prescription and/or dispensing of the medicine and the centre's therapeutic protocol". The use of off-label medicines must be authorised by the competent bodies of the health services of the autonomous regions[56].

In addition, the RD 1015/2009 allows medicines not authorised in Spain but authorised in other countries to be used provided the following conditions:

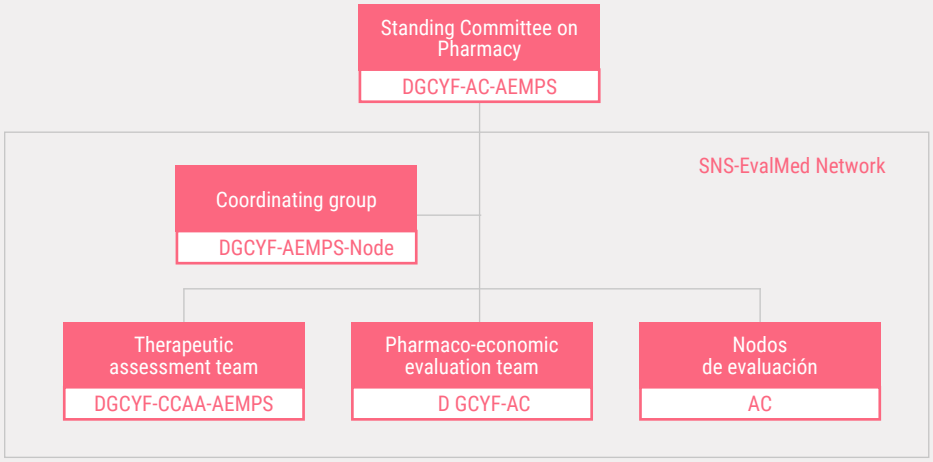
a) There are no medicines authorised in Spain with this composition or the pharmaceutical form authorised is not suitable for the treatment of the patient.

b) There is no authorised medicinal product in Spain that provides a suitable alternative for that patient.

With regard to the evaluation of medicines, Therapeutic Positioning reports (TPR) were introduced in 2013, with the aim of increasing the coherence, efficiency, integration and continuity of the different evaluations of the same medicine, guaranteeing independence and contributing to the rational use of medicines and equity in patient access[57].

Subsequently, in 2020, the Ministry of Health published the Plan for the Consolidation of TPRs in the NHS, which aimed was to establish the TPR as a reference tool for positioning and introduced economic evaluation in these types of reports. This plan, also promoted the creation of the medicine's evaluation network, called REvalMed, consisting of a therapeutic evaluation group, an economic evaluation group and seven evaluation nodes (one of them focused non-oncological RD), who were appointed by the Autonomous Communities and who were designed as reviewers (Figure 10)[58].

Figure 10. Outline of the structure of the REvalMed until 2023



Source: *AEMPS (2020)*[58]

However, in 2023 the National Court annulled, due to legal defects, the aforementioned Consolidation[59], which obliged the AEMPS to change the structure and format of the TPRs, adapting them to the provisions of the National Court ruling and returning to the format established in 2013[60].

With regard to the price and reimbursement of OMPs, the resolution of 2 June 2020 of the Directorate General for the Common Portfolio of Services of the National Health System and Pharmacy establishes that medicines classified as orphan drugs are excluded from the Reference Price System[l], with the aim of favouring the economic interest of companies in marketing their products in the country, as well as avoiding stock-outs of some medicines for RDs[61]. Moreover, according to the Royal Decree Law 8/2010 which adopted extraordinary measures for the reduction of the public deficit, all medicines paid for by the National Health System through the pharmacy services of hospitals, health centres and primary care structures will be subject to a deduction of 7.5% of the purchase price, which shall be 4% in the case of a OMP[62].

On the other hand, the order SSI/2065/2014 specified the inclusion of seven endocrine-metabolic diseases: congenital hypothyroidism, phenylketonuria, cystic fibrosis, medium-chain acyl-coenzyme A dehydrogenase deficiency (MCADD), long-chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency (LCHADD), glutaric acidaemia type I (GA-I), and sickle cell disease in in the Common Portfolio of Health Care Services of the Spanish NHS NSP[63].

Finally, it is worth highlighting the growing importance that the use of data technology and AI has and will have in the future in the healthcare context and especially in the context of the RDs. In Spain, the Ministry of Economic Affairs and Digital Transformation launched the so-called National Artificial Intelligence Strategy, which included the following strategic objectives[64]:

- Boosting scientific research and technological development
- Promoting the development of digital talents and skills
- Developing data platforms and technology infrastructures to support AI
- Integrating AI into value chains

l *The Reference Pricing System is based on the maximum price at which each presentation of a medicine can be sold, with an annual review system that can lead to a mandatory price decrease.*

- Enhancing the use of AI in public administration
- Establishment of an ethical and normative framework that strengthens the protection of individual rights, in order to ensure social inclusion and welfare.

➜ Strategies for RDs

Spain relies on a national and various regional strategies which aim at improving prevention, diagnosis and care for people with RDs.

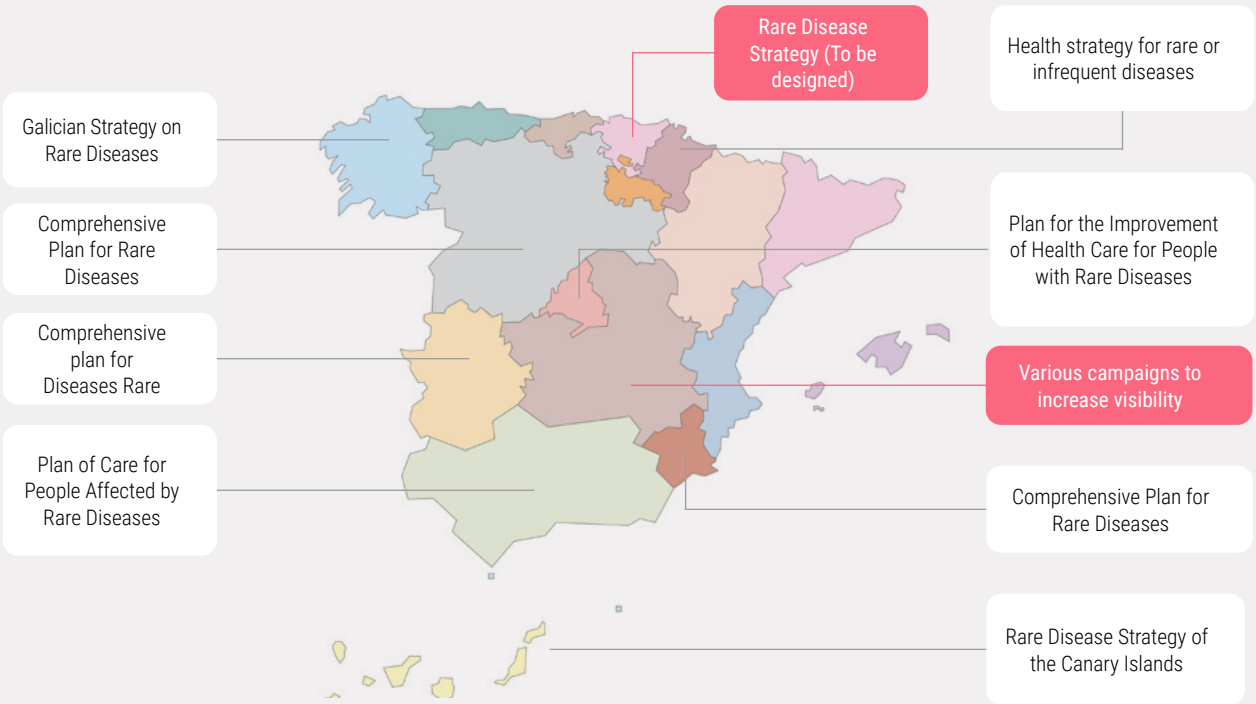
National strategy

In 2009, the Interterritorial Council of the Spanish NHS approved the National Strategy for Rare Diseases, which aimed to improve the care and treatment of these diseases. In order to re-evaluate the results obtained and adjust to the new realities, the Strategy was updated in 2014, including 7 strategic lines[65]:

1. Information on rare diseases. The importance of providing accurate information to professionals, patients and relatives is emphasised in order to improve diagnosis and social and health care. The importance of registries as a fundamental tool in the case of RDs is also highlighted, due to their low incidence, high dispersion and level of ignorance. The most important milestone is the creation of the Epidemiological Network for Research on Rare Diseases, dependent on the Carlos III Institute, which served as the basis for the Spanish Network of Rare Disease Registries for Research (SpainRDR), which, together with the Autonomous Regions, is responsible for the creation of the National Registry of Rare Diseases[66].
2. Prevention and early detection. The importance of prevention is emphasised, with genetic diagnosis and neonatal screening programmes as the first line of rapid diagnosis.
3. Health care. Emphasis is placed on rehabilitation in patients with RDs and on having Centres of Reference Services and Units (CSUR).
4. Therapies. Reference is made to the development of advanced therapies, in particular at the genetic level and the use off-label of therapeutic alternatives.
5. Socio-health care. Measures are envisaged to improve socio-health care, with the example of the Public System of Equal Opportunities for People with Disabilities.
6. Research. The importance of information flow between the different research networks, both at national and European level.
7. Training. The importance of the approach to RDs in the training process is highlighted, in both primary care and hospital care, with primary care perhaps being the area in which the greatest dedication is required.

In addition to this National Strategy, several Autonomous Communities have developed specific regional plans and strategies for their region. Some of them have strategic areas/lines similar to those of the National Strategy, while others have incorporated specific measures to address RDs in their territory (Figure 11).

Figure 11. Geographical distribution of the regional plans and strategies on RDs



Source: *own elaboration*

Andalusia

In 2008, the Andalusian Regional Government launched the 2008-2012 Plan for the Care of People Affected by Rare Diseases, with the definition of 5 specific objectives and 33 actions to achieve these objectives[67]:

- Increasing epidemiological knowledge on RDs
  - To have a Clinical-Epidemiological Register of RDs linked to the care units and services, which is compatible with the corporate information systems
  - Contribute to the promotion of research activity in relation to the RDs
  - To have an RD web page within the health portal with the orientation and contents defined in this plan
- Improving the access of affected people to safe, quality care
  - Establishment of a catalogue of health resources for RDs, indicating designated and accredited reference centres
  - To have a social and health care manual defining the activities of the Social Work Network and its coordination with other departments and social services
  - Potential reference centres for RDs will be identified and their designation and accreditation will be carried out in accordance with the relevant national and regional regulations
  - Establishment of the Observatory for Medicines and Medical Devices needed for the treatment of RDs
  - Launching of the Advisory Committee of Experts on the treatment of RDs and OMPs

- Improving knowledge management in rare diseases, professionals' training and fostering research
  - Definition of a training strategy in RDs, jointly with the Genetics Plan and in relation to the CIBERER activities
  - Promote national and international research projects on RDs involving Andalusian professionals
  - Promoting joint projects between the Andalusian Public Health System and FEDER for the evaluation of quality of life and satisfaction with the health care received
- Develop up-to-date information on rare diseases of interest to affected persons, health professionals and society in general
  - Define a plan for the development of guidelines for the care of RDs
  - Keeping track of the general guidelines by disease group and of specific guidelines that have been produced according to the development plan
- Recognising the specificity of rare diseases and addressing them in the health system with a global strategy and with the participation of patient associations
  - Each RD that is addressed by a specific clinical guideline including its evolutionary characteristics and its possible impact on the functionality of the affected person
  - Analysing the needs of each disease and the other products needed to treat it and seeking alternatives to ensure access under equitable conditions
  - Analysis of the procedures and the level of transfer aid to receive health care in the reference centres when patients are outside their place of residence

Extremadura

Extremadura was the pioneer region in approving a document focused on RDs, with the publication in 2004 of the Book on Rare Diseases in Extremadura[68]. It also approved the Comprehensive Plan for Rare Diseases in Extremadura in 2010 and updated it in 2019[69,70]. The latter plan details 16 proposed objectives, organised into 8 areas of intervention and 77 lines of action (Table 2)[70].

Table 2. Areas of intervention and specific objectives of the PIER in Extremadura

Information area of RDs	
Objetive 1.	To provide information on RDs and available resources to affected people and their families, to professionals from the different areas involved, and to the general public.
Objetive 2.	To strengthen coordination between the different levels of care at regional, national and international level to inform about the resources available in RDs.
Area of primary prevention and early detection	
Objetive 3.	Develop primary prevention strategies aimed at reducing the incidence of RDs.
Objetive 4.	Early detection of cases of RDs, with criteria of equity and accessibility.
Information systems area	
Objetive 5.	To increase epidemiological knowledge of RDs in Extremadura.
Healthcare area	
Objetive 6.	To guarantee healthcare for people with RDs by favouring continuity of care and accessibility to the necessary resources.
Objetive 7.	To structure an integrated network to extend specific attention to RDs in the Autonomous Region of Extremadura.
Objetive 8.	To enhance humanisation in comprehensive healthcare for patients with RDs and their families.
Treatment area	
Objetive 9.	To ensure timely and appropriate accessibility of orphan medicinal products necessary for the treatment of RDs throughout country, as well as medical devices, adjuvants, curative materials, medical devices and dietary therapeutic products for people affected by an RD.
Objetive 10.	Strengthen research and development of orphan drugs and highly complex treatments.
Integral care area (education and social)	
Objetive 11.	To facilitate, speed up and normalise the schooling process for pupils with RDs.
Objetive 12.	To inform, train and raise awareness in the educational community about RDs in order to bring the problem of RD closer to the educational context and achieve the inclusion of children with RDs during the school stage and their social normalisation, incorporating new knowledge and rethinking beliefs and fears.
Objetive 13.	To improve accessibility in the processes of recognition of the degree of disability and dependency in the cases of people affected by RDs.
Objetive 14.	To improve the coverage of services aimed at community integration, increasing personal autonomy and supporting the family and social network of people with RDs in a situation of dependency.
Training area	
Objetive 15.	Promote training in RDs for professionals and those involved in the care of patients with RDs.
Research area	
Objetive 16.	Promote and disseminate research on renewable energy sources.

Note: ***RDs:*** *rare diseases.*

Source: *Junta de Extremadura (2019)*[70]

Canary Islands

In 2021, the Canary Islands health authorities published the Canary Islands Rare Diseases Strategy 2022-2026, with the aim of guaranteeing a comprehensive approach to people diagnosed with or suspected of having a rare disease, allowing equitable access to coordinated care that favours early diagnosis, as well the availability of treatments within the autonomous community.

To achieve this objective, the strategy is articulated in 7 strategic lines that are developed in 16 projects (Figure 12)[71].

Figure 12. Strategic lines and projects of the Canary Islands Rare Disease Strategy

Strategic lines

1. Rare disease registry and information systems
- RDs Registry
- Adaptation of information systems to the specificity of RDs

2. Prevention and early diagnosis
- Primary prevention preconception and during pregnancy
- Early detection and diagnosis
- Strengthening clinical genetics reference units and specialised consultations for rare diseases

3. Organisation of health care
- Care for people with rare diseases
- Improving paediatric patient care
- Promoting humanisation in rare disease care

4. Comprehensive approach in coordination with other areas of care
- Coordination with other social protection systems to ensure a comprehensive approach to people with rare diseases
- Enhancing the role of patient associations and social support
- Patient and family education support

5. Access to treatment
- Access to medicines and other health products
- Rehabilitation and other complementary treatments

6. Research and training for professionals
- Training and awareness-raising for professionals
- Research

7. Public awareness and education
- Raising the awareness of the general population about RDs

Source: *own elaboration based on Servicio Canario de Salud (2021)*[71]

Castilla y León

In 2023, Castilla y León has published its Comprehensive Plan for Rare Diseases, whose main objective is to promote the development of a coordinated model of comprehensive care that guarantees timely and equitable access to people with RDs and without diagnosis as well as their families, through an effective and efficient management of resources, in order to reduce morbidity and mortality and cover specific needs to improve their quality of life.

To this end, this plan has 7 strategic lines encompassing 25 projects and 71 different actions. A summarised version of these strategic lines is shown in Figure 13[72].

Figure 13. Summary of the strategic lines set out in the Castilla y León Integrated RDs Plan

1. **Information systems and registration**
   Promote the development of information systems in the field of RDs by strengthening the existing RD Registry of Castilla y León and favouring the provision of coding systems for these diseases
2. **Prevention and early diagnosis**
   Promote prevention activities and reduce diagnostic times to favour early diagnosis, through the protocolisation of diagnostic tests and favouring access to genetic counselling
3. **Integrated care model**
   Promote a comprehensive approach to people with RDs and those without a diagnosis, focusing on precision personalised medicine and promoting a network structure through Units, Reference Care Nodes and Multidisciplinary Reference Teams
4. **Care focused on people with undiagnosed RDs and their families**
   Promote care from a human perspective and focused on people with Rare and Undiagnosed Diseases and their families, which reduces displacement and guarantees continuity of care, taking into account the demographic and geographic particularities of the autonomy
5. **Treatments**
   Facilitate access, in conditions of equity, to specific treatments and health products for RDs, considering the demographic and geographic particularities of the autonomous region
6. **Research**
   Promote the development of RDs research activities and facilitate networking at regional level for the identification of common strategies, as well as with other national and international research structures and groups
7. **Information and training**
   To promote the improvement of knowledge about RD through the dissemination of updated information and the development of continuous training activities aimed at professionals, people with and without RD, their families and other organisations involved

Surce: *own elaboration based on Sanidad Castilla y León (2023)*[72]

Galicia

In recent years, Galicia has also published a specific plan for RDs, the Galician Rare Diseases Strategy, with the aim of establishing a new optimised model of care for RDs, based on homogeneous criteria to guarantee shorter diagnosis times, less variability in patient management, and more coordinated and efficient management. Figure 14 shows a summary of the strategic axes and the objectives to be met in each axis included in the strategy[73].

Figure 14. Summary of the objectives included in the Galician Rare Diseases Strategy

1 **Development of the Galician Rare Diseases Register**

Objectives: to standardise and record information related to RDs in Galicia, providing epidemiological data on their incidence and prevalence, as well as their associated determinants

2 **Strengthening primary and secondary prevention**

Objectives: to ensure the primary and secondary prevention of RDs by prioritising the prevention of the transmission of inherited diseases from parents to offspring through assisted human reproduction techniques, to give 100% of newborns access to the screening tests included in the programme and to reduce the time to diagnosis, among other things

3 **Standardisation of health care**

Objectives: to define the new care model, to overcome the difficulty of identifying the initial suspicion of a possible pathology, the fragmentation of knowledge and the frequent inefficiency of the tests carried out, and to organise care by implementing a new care model for patients with RDs

4 **Improving access to pharmacological and non-pharmacological therapies**

Objectives: to facilitate access to the necessary treatments for people affected by rare diseases, be it orphan drugs, conventional drugs, advanced therapies, investigational drugs, artificial nutrition or medical devices

5 **Promoting socio-health coordination and citizen participation**

Objectives: to optimise coordination between health and social policies, including the identification and development of all synergies that contribute to increasing the autonomy of patients with RDs, alleviating their limitations or suffering and facilitating their social reintegration

6 **Promotion of training and dissemination among professionals, patients and citizens**

Objectives: to train health personnel and disseminate knowledge about RDs among health professionals as well as informing patients, families and carers

7 **Promoting research and health outcomes**

Objectives: To dynamize the research and innovation structure of the Galician public health system in order to increase the participation and collaboration of Galician health research groups in R&D lines related to RDs, to disseminate research results and to guide and joint efforts to achieve health results

Source: *Xunta de Galicia (2021)*[73]

Madrid

The Community of Madrid also developed a specific strategy for RDs, with the publication in 2016 of the Plan for the Improvement of Health Care for People with Rare Diseases. The general objective of the plan was to improve care for people with rare diseases to reduce morbidity and mortality and to improve their quality of life, through comprehensive healthcare. The plan sets out 8 lines of strategy with 10 specific objectives for each line encompassing 123 actions (Figure 15)[74]. This plan, stipulated for the period 2016-2020, is expected to be updated during 2023[74].

Figure 15. Objectives and strategic lines set out in the Plan for the Improvement of Health Care for People with Rare Diseases in the Region of Madrid, 2016-2020

Strategic lines

1. Information systems on RDs: resources, registers and information systems
- Improving accessibility to resource information for affected people, families and professionals.
- To have quality epidemiological information available to improve knowledge of rare diseases.
- To have a comprehensive information system for the planning, management, evaluation and monitoring of strategic actions in rare diseases

2. Prevention and early diagnosis
- Promote the prevention of RDs, early diagnosis and access to genetic counselling for those affected and their families

3. Health organisation. Units of Expertise, Centres, Services and Reference Units: coordination and network collaboration
- To have key elements that enable the development of comprehensive health care with adequate coordination between the different levels of care and network collaboration of the Centres, Services, Reference Units and Experience Units

4. Therapies: orphan drugs, adjuvants and medical devices
- Facilitating access to therapies and medical devices

5. Inter-agency coordination for comprehensive care
- A better coordination of health agents with the different social agents involved in the care of those affected by rare diseases in order to provide adequate comprehensive care

6. Research
- To plan and promote research on rare diseases, the cooperation between research structures at regional, national and international level and the approach and integration of society in the field of research on these diseases

7. Training
- Promote awareness and training of health care professionals, facilitate knowledge of early diagnosis, access to information on socio-health resources and improve information to those affected and their families

8. Participation and partnership
- Encourage the participation of those affected and their families in the design and development of the actions to be carried out, through the associative movement

Fuente: *compiled by author based on Comunidad de Madrid (2016)*[74]

Murcia

In 2018, the Region of Murcia published its Comprehensive Plan for Rare Diseases, which included a set of measures to understand RD patients' expectations, and improve knowledge, care, coordination and research on rare diseases. This plan includes more than 100 lines of action to achieve 42 specific objectives (Figure 16)[75].

Figure 16. Summary of the strategic lines set out in the Comprehensive Plan for Rare Diseases in the Region of Murcia

1. **Epidemiology**
   These strategic lines include 4 objectives, related to the improvement of the RDIS and the quality of information and epidemiological analysis of rare malignant tumours and mortality due to RDs. To this end, 15 lines of action are set out
2. **Information**
   Guaranteeing access to general information on RDs and the resources available in the region in the health, education, employment and social spheres, and increasing the visibility of RDs and the degree of public awareness, are the two objectives set out in this strategic line for which 7 lines of action have been established
3. **Prevention, early detection and diagnosis**
   In this line, 5 objectives are set out, ranging from reducing the incidence of those RDs that could benefit from prevention programmes, improving prenatal screening and diagnosis programmes and genetic counselling, among others. In order to achieve these objectives, 18 lines of action are indicated
4. **Health care**
   The 4 objectives of this strategic line are: to guarantee the best care for people with RDs, to establish the regional model for the health care of these patients, to ensure continuity of care and to guarantee access to other health care devices. To this end, 16 lines of action are indicated
5. **Therapeutic resources**
   This line brings together 6 objectives, ranging from facilitating access to medical devices, equipment, medical devices and others for people affected by a rare disease, to strengthening the area of rehabilitation in the care of these patients, to promoting safe access to advanced therapies for these patients
6. **Education**
   The 5 objectives of this line are: i) to inform and raise awareness in the educational community about RDs; ii) to improve the information available on RDs; (iii) to identify as early as possible the educational needs of pupils with RDs; (iv) to provide adapted education; (v) to coordinate educational, health and social actions for pupils in the school context. 24 lines of action were set out to achieve these objectives
7. **Social services**
   These strategic lines of action include 8 objectives, among which are to promote access to social services for those affected by RDs, to improve economic aid to attend to socio-family needs or individual aid for patients and to promote the associative movement, among others. The number of lines of action proposed is 28
8. **Social and health coordination**
   Drawing up a protocol for social and health coordination in the care of people suffering from a rare disease and their relatives and improving communication between professionals and favouring networking are the two objectives set out in this strategic line. At the same, 8 lines of action are marked out
9. **Training**
   The 3 objectives of this strategic line are: to increase the knowledge of RDs in undergraduate training, to deepen the notion and management of RDs in postgraduate training and to promote continuous training. 23 lines of action are indicated to achieve these objectives
10. **Training**
    The 3 objectives of this line are to promote research projects to improve diagnosis, to promote research into treatments and to develop lines of research into the epidemiology of RDs. To achieve these objectives, 23 lines of action are indicated

Note: ***RDs:*** *Rare Diseases;* ***RDIS:*** *Rare Disease Information System.*

Source: *own elaboration based on Región de Murcia (2018)*[75]

Navarre

In the Autonomous Community of Navarre, the Health Strategy for Rare or Infrequent Diseases was published in 2017 with the following objectives[76]:

- Promoting the prevention of RDs
- Promoting clinical suspicion and speeding up diagnosis
- Providing a comprehensive, coordinated continuum of care
- Increasing functional capacity and improving accessibility to rehabilitative care
- Activation, training, empowerment and co-responsibility of patients and families.
- Stimulate the training of professionals in the field of RDs.
- Improving Registration and Reporting of RDs cases
- Promoting RDs research

The lack of available information from the community doesn't allow us to describe these measures in more details.

Actions in other Autonomous Communities

In addition, other Autonomous Regions have formalised other types of measures which, although they cannot be defined as an RD plan or strategy, give special attention to this type of pathologies in their territories.

For example, Castilla la Mancha has carried out several campaigns to increase the visibility of RDs, and launched a website with information on neonatal screening, social resources available to patients with RDs, patient registry, training and patient associations, among others[77].

In the Basque Country, one of the objectives of the 2023-2025 Strategic Plan includes the promotion of care centred on patients' needs and expectations through specific plans, including the creation of a strategy for rare diseases, although this has not been designed yet[78].

➜ RDs registers in Spain

Spain has different networks and registries. The Rare Diseases Patient Registry, belonging to the ISCIII, is coordinated and managed by the Institute for Research on Rare Diseases (IIER), which is part of the CIBERER (Consortium for Biomedical Research in Rare Diseases Network). From a legal point of view, this registry is based on the SCO/1730/2005 order, which establishes the criteria for its creation and operation, the place where the legal custody and responsibility of the registry must be deposited. More than 23,000 patients are currently enrolled in this register[79].

The patient register consists of two basic pillars. First, it offers patients themselves or their guardians (in the case of children and people with disabilities) the opportunity to register individually and motu proprio in this register. This option gives patients access to specific information of their disease, as well as the opportunity to participate to online studies regarding the use of medicines, quality of life, dependency analysis, use of health resources and donation of samples to the IIER sample bank, among others[79]. Furthermore, it offers researchers and health professionals a place from which to manage the rare disease under their scientific interest. This management is carried out in collaboration with the administrators of the system at the ISCIII-IIER and has the necessary guarantees of confidentiality and security. This register has two different data entry channels:

- Outcome-oriented patient registries: Data provided by the patients themselves (see instructions on the Registration button and in the user manual).
- Data provided by professionals participating in research networks and medical societies that have an agreement with the ISCIII.

On the other hand, in 2015, the ReeR was created for 3 purposes[80]:

- To provide epidemiological information on RDs, their incidence and prevalence and their associated determinants.
- To provide the necessary information to guide the planning, health management and evaluation of preventive and care activities in the field of RDs.
- To provide basic indicators on rare diseases that allow comparison between ACs and with other countries.

In 2022, the Ministry of Health published a report on RDs which included data provided by 76% of the Autonomous Communities (Andalusia, Aragon, Balearic Islands, Canary Islands, Castilla y León, Catalonia, Valencia, Galicia, Community of Madrid, Region of Murcia, Foral Community of Navarre, Basque Country and La Rioja) and covers 90% of the Spanish population. It also included 22 rare pathologies that affect 28,397 patients of which 15,695 men and 12,702 women (Table 3)[81].

Table 3. Number of live cases as of 1 January 2020 by sex

Name of the Rare Disease	Men	Women	Total
Friedreich's ataxia	300	352	652
Proximal spinal muscular atrophy	278	240	518
Tuberous Sclerosis Complex	906	1,000	1,906
Renal Dysplasia	1,049	644	1,693
Steinert's Myotonic Dystrophy	1.771	1,863	3,634
Fabry disease	190	202	392
Gaucher disease	116	94	210
Huntington's disease	715	884	1,599
Niemann Pick disease	46	28	74
Rendu Osler disease	574	833	1,407
Wilson's disease	492	401	893
Amyotrophic Lateral Sclerosis (ALS)	1,193	895	2,088
Phenylketonuria	627	774	1,401
Cystic Fibrosis	1,587	1,559	3,146
Haemophilia A	2,760	418	3,178
Osteogenesis Imperfecta	568	626	1,194
Angelman Syndrome	164	166	330
Beckwith Wiedemann syndrome	173	144	317
Goodpasture Syndrome	171	18	389
Marfan syndrome	827	739	1,566
Prader Willi Syndrome	426	407	833
Fragile X syndrome	762	215	977
TOTAL	15,695	12,702	28,397

Source: *Ministry of Health (2022)*[81]

Bibliographical references

1. Novoa F, Cabello JF. Ethics of equity and justice in access to diagnosis, treatment and rehabilitation of patients with rare diseases. Rev Médica Clínica Las Condes. 2015;26(4):527-32, doi: 10.1016/j.rmclc.2015.06.027.
2. Senate and House of Representatives of the United States of America in Congress assembled. Orphan Drug Act. Public law 97-414. 1983.
3. Food and Drug Administration. Small Business Assistance: Frequently Asked Questions for New Drug Product Exclusivity. FDA. 2018.
4. Maher PD, Haffner M. Orphan Drug Designation and Pharmacogenomics: Options and Opportunities. BioDrugs. 2006;20(2):71-9, doi: 10.2165/00063030-200620020-00001.
5. Seoane-Vazquez E, Rodriguez-Monguio R, Szeinbach SL, Visaria J. Incentives for orphan drug research and development in the United States. Orphanet J Rare Dis. 2008;3(1):33, doi: 10.1186/1750-1172-3-33.
6. FDA. Developing Products for Rare Diseases & Conditions. FDA. [accessed 28 September 2020]. Available at: https://www.fda.gov/industry/developing-products-rare-diseases-conditions.
7. Nagaraja S, Balamuralidhara V, Jyothi M, Ragunandhan H. V. Orphan Drug Regulation In Japan and Australia. Int J Res Pharm Sci. 2020;11(2):1831-9, doi: 10.26452/ijrps.v11i2.2088.
8. Administration AGD of HTG. Orphan Drug designation eligibility criteria. Therapeutic Goods Administration (TGA). [accessed 29 Sept. 2020]. Available at: https://www.tga.gov.au/publication/orphan-drug-designation-eligibility-criteria.
9. European Council, European Parliament. Regulation (EC) No 141/2000 on orphan medicinal products. 2000.
10. EMA - European Medicines Agency. The evaluation of medicines, step-by-step. European Medicines Agency. [accessed 30 October 2020]. Available at: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/evaluation-medicines-step-step.
11. Spanish Agency for Medicines and Health Products. How medicines and health products are regulated in Spain. 2014.
12. Hernández Garcia C. Rare diseases in Spain: regulatory aspects. Libro blanco de las enfermedades raras en España. Madrid: Gaspar Casal Foundation; 2018. p. 218.
13. European Medicines Agency. Orphan designation: Overview. Available at: https://www.ema.europa.eu/en/human-regulatory/overview/orphan-designation-overview.
14. European Union. Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. Available at: https://op.europa.eu/en/publication-detail/-/publication/e9a9fff0-dbd9-11ea-adf7-01aa75ed71a1/language-en.
15. EMA. Orphan incentives. European Medicines Agency. [accessed 1 October 2020]. Available at: https://www.ema.europa.eu/en/human-regulatory/research-development/orphan-designation/orphan-incentives.
16. European Commission. Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. 2020.
17. EMA. Orphan medicines figures 2000-2019. 2020.
18. EMA. Download medicine data. Available at: https://www.ema.europa.eu/en/medicines/download-medicine-data.
19. Official website of the European Union. European Reference Networks. Public Health - European Commission. [accessed 15 October 2020]. Available at: https://ec.europa.eu/health/ern_es.
20. Neez E, Gentilini A, Dutton R, Hutchings A. Estimated impact of EU Orphan Regulation on incentives for innovation. DOLON; 2020.
21. European Commission. A pharmaceutical strategy for Europe. [accessed 28 September 2023]. Available at: https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe_en.
22. Communication from the Commission to the European Parliament, the Council, European Economic and Social Committee and Committee of the Regions Pharmaceutical Strategy for Europe. 2020.

23. European Commission. Review of the general pharmaceutical legislation of the Union. European Commission - Have your say [accessed 28 September 2023]. Available at: https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12963-Revision-de-la-legislacion-general-farmaceutica-de-la-Union_es.

24. Evaluation of the medicines for rare diseases and children legislation. [accessed 28 September 2023]. Available at: https://health.ec.europa.eu/medicinal-products/medicines-children/evaluation-medicines-rare-diseases-and-children-legislation_en.

25. European Commission. Proposal for a directive of the european parliament and of the council on the Community code relating to medicinal products for human use and repealing Directive 2001/83/EC and Directive 2009/35/EC. 2023.

26. Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU (Text with EEA relevance). vol. 458. vol. 458. 2021.

27. Global Legal Insights. Pricing & Reimbursement Laws and Regulations| EU Health Technology Assessment Regulation| GLI. GLI - Global Legal Insights - International legal business solutions. [accessed 28 September 2023]. Available at: https://www.globallegalinsights.com/practice-areas/pricing-and-reimbursement-laws-and-regulations/01-eu-health-technology-assessment-regulation.

28. Official Journal of the European Union. Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU (Text with EEA relevance). vol. 458. vol. 458. 2021.

29. Joint clinical assessment in the EU: Pan-European HTA for drugs and medical devices will become reality. [accessed 28 September 2023]. Available at: https://www.xcenda.com/insights/htaq-spring-2022-joint-clinical-assessment-eu.

30. Remap Consulting. What is the joint clinical assessment and what does it entail? [accessed 28 September 2023]. Available at: https://remapconsulting.com/hta/what-is-the-joint-clinical-assessment-and-what-does-it-entail/.

31. Garc'a Lopez JL, del Llano JE, del Diego J, Recalde JM. Contribution of Real World Data (RWD) to the improvement of clinical practice and resource consumption of patients. Gaspar Casal Foundation; 2014.

32. European Platform on Rare Disease Registration. [accessed 29 September 2023]. Available at: https://eu-rd-platform.jrc.ec.europa.eu.

33. Orphanet. Rare Disease Registries, cohorts and databases. 2023.

34. European Commission. Commission Implementing Decision of 10.3.2014 laying down criteria for the establishment and evaluation of European Reference Networks and their members, and facilitating the exchange of information and expertise in the establishment and evaluation of such networks. 2014.

35. Ministry of Health. Cross Border Healthcare in the EU - Rare Diseases (included and not included in European reference networks). [accessed 28 September 2023]. Available at: https://www.sanidad.gob.es/pnc/redes/home.htm.

36. MHRA. Orphan medicinal products. GOV.UK. [accessed 28 September 2023]. Available at: https://www.gov.uk/guidance/orphan-medicinal-products-in-great-britain.

37. Graham L, Srinivasan R. Orphan Drugs in the EU/EEA and UK. J Kemp. 2023.

38. Global Legal Insights. Pricing & Reimbursement Laws and Regulations. United Kingdom. [accessed 21 July 2021]. Available at: https://www.globallegalinsights.com/practice-areas/pricing-and-reimbursement-laws-and-regulations/united-kingdom.

39. Montague R. The NICE HST process (2/3) - differences in assessment of cost-effectiveness between the HST and STA. Source Health Economics. [accessed 28 September 2023]. Available at: https://source-he.com/the-nice-hst-process-2-3-differences-in-assessment-of-cost-effectiveness-between-the-hst-and-sta/.

40. Campillo-Artero C, Ortœn V. Cost-effectiveness analysis: why and how. Rev Esp Cardiol. 2016;69(4):370-3, doi: 10.1016/j.recesp.2016.01.013.

41. Matar M, Tatham G, Calderwood S, Girn S. NICE's Highly Specialized Technologies. Simon-Kucher. [accessed 27 July 2021]. Available at:: https://www.simon-kucher.com/en/blog/nices-highly-specialized-technologies.

42. Genetic Alliance UK. Changes to the HST programme. [accessed 28 July 2021]. Available at: https://geneticalliance.org.uk/gauk-news/news/changes-to-the-hst-programme/.

43. NICE. Consideration of the evidence. Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2. [accessed 14 October 2021]. Available at:: https://www.nice.org.uk/guidance/hst12/chapter/4-Consideration-of-the-evidence#applying-qaly-weighting-2.

44. SMC. Guidance to Submitting Companies for Completion of New Product Assessment Form (NPAF). Supplement for medicines for extremely rare conditions (ultra-orphan medicines). Available at: https://www.scottishmedicines.org.uk/media/6168/guidance-su- pplement-ultra-orphan.pdf.

45. SMC. SMC modifiers used in appraising new medicines. Available at: https://www.scottishmedicines.org.uk/media/3565/modifiers.pdf.

46. Ministry of Health and Prevention. Autorisations d'accès précoce (ex-ATU) : montants des indemniés maximales. Ministry of Health and Prevention. [accessed 29 September 2023]. Available at: https://sante.gouv.fr/ministere/acteurs/instances-rattachees/comite-economique-des-produits-de-sante-ceps/article/autorisations-d-acces-precoce-ex-atu-montants-des-indemnites-maximales.

47. Rudd A. What do France's ATU reforms mean for manufacturers? Remap Consulting. [accessed 29 September 2023]. Available at: https://remapconsulting.com/early-access/what-do-frances-atu-reforms-mean-for-manufacturers/.

48. Deutscher Bundestag. Finanzreform der gesetzlichen Krankenversicherung beschlossen. Deutscher Bundestag. [accessed 28 February 2023]. Available at: https://www.bundestag.de/dokumente/textarchiv/2022/kw42-de-gkv-finanzierungsstabilisierungsgesetz-916742.

49. IQWiG. Drug approval and early benefit assessment in Germany. [accessed 7 September 2021]. Available at: https://www.iqwig.de/presse/im-fokus/neue-arzneimittel-zulassung-nutzenbewertung-erstattung/1-arzneimittel-zulassung-und-fruehe-nutzenbewertung-in-deutschland/.

50. Organisation for Economic Co-operation and Development (OECD). Pharmaceutical reimbursement and pricing in Germany. 2018.

51. Verband Forschender Arzneimittelhersteller (VFA). Stellungnahme zum Gesetzentwurf fŸr ein GKV- inanzstabilisierungsgesetz (GKV-FinStG). 2022.

52. Farmaci orfani. [accessed 29 September 2023]. Available at: https://aifa.gov.it/farmaci-orfani.

53. Tarantola A, Otto MH, Armeni P, Costa F, Malandrini F, Jommi C. Early access programs for medicines: comparative analysis among France, Italy, Spain, and UK and focus on the Italian case. J Pharm Policy Pract. 2023;16(1):67, doi: 10.1186/s40545-023-00570-z.

54. Agenzia Italiana del Farmaco. Farmaci innovativi. [accessed 9 June 2021]. Available at: https://aifa.gov.it/farmaci-innovativi.

55. Government of Spain. BOE-A-2015-8343. Real Decreto Legislativo 1/2015, de 24 de julio, por el que se aprueba el texto refundido de la Ley de garant'as y uso racional de los medicamentos y productos sanitarios. Available at: https://www.boe.es/buscar/act.php?id=-BOE-A-2015-8343.

56. Independent Authority for Fiscal Responsibility. Hospital spending in the national health system: pharmacy and investment in capital goods. 2019.

57. Garc'a V, Corbal‡n L, Baquero S, Garc'a-Esquinas E, Sacrist‡n JA. Therapeutic positioning reports: experience in Spain in the period 2013-2019. Aten Primaria. 2020;52(10):697-704, doi: 10.1016/j.aprim.2020.02.012.

58. Ministry of Health. Presentation of the plan for the consolidation of the Therapeutic Positioning Reports (TPR) of medicines in the National Health System (NHS). 2020.

59. Audiencia Nacional. Contentious-Administrative Chamber. Eighth Section. Appeal 0000123/20213. 2023.

60. Arganda C. La Aemps assumes the sentence that annulled Revalmed and changes the IPTs @diariofarma. diariofarma. [accessed 24 October 2023]. Available at: https://diariofarma.com/2023/09/10/la-aemps-asume-la-sentencia-que-anulo-revalmed-y-cambia-los-ipt.

61. Directorate General for the Common Portfolio of Services of the National Health System and Pharmacy. Resolution of 2 June 2020.

62. BOE-A-2010-8228 Royal Decree-Law 8/2010, of 20 May, adopting extraordinary measures to reduce the public deficit. [accessed 29 September 2023]. Available at: https://www.boe.es/buscar/act.php?id=BOE-A-2010-8228.

63. Ministry of Health, Social Services and Equality. Order SSI/2065/2014, of 31 October, amending Annexes I, II and III of Royal Decree 1030/2006, of 15 September, which establishes the portfolio of common services of the National Health System and the procedure for its updating. vol. BOE-A-2014-11444. vol. BOE-A-2014-11444. 2014.

64. Ministry of Economic Affairs and Digital Transformation. National Artificial Intelligence Strategy. Third Vice-Presidency of the Government. 2020.

65. Ministry of Health, Social Services and Equality. Rare Diseases Strategy of the National System. Update approved by the Interterritorial Council of the National System. 2014.

66. FEDER. Pages - Epidemiology of Rare Diseases. [accessed 1 October 2020]. Available at: https://www.isciii.es/QuienesSomos/Centros-Propios/IIER/AreaEpidemiologia/EpidemiologiaEnfermedadesRaras/Paginas/default.aspx.

67. Regional Government of Andalusia. Plan de Atención a Personas afectadas por Enfermedades Raras. [accessed 14 September 2023]. Available at: https://www.juntadeandalucia.es/organismos/saludyconsumo/areas/planificacion/planes-integrales/paginas/paper.html.

68. Regional Government of Extremadura. Rare diseases in Extremadura. 2004.

69. Regional Government of Extremadura. Integral Plan for Rare Diseases in Extremadura. 2010.

70. Regional Government of Extremadura. Integral Plan for Rare Diseases in Extremadura 2019-2023. Available at: https://www.juntaex.es/w/actuacion-plan-integral-de-enfermedades-raras-de-extremadura-pier-2019-2023.

71. Government of the Canary Islands. Rare Diseases Strategy of the Canary Islands. Disponible en: https://www3.gobiernodecanarias.org/sanidad/scs/contenidoGenerico.jsp?idDocument=778a51b8-17bb-11ed-8a1a-1b6e6a9a9edd&idCarpeta=61e907e3-d473-11e9-9a19-e5198e027117.

72. Regional Government of Castilla y León. Plan Integral de Enfermedades Raras de Castilla y León (PIERCYL) 2023-2027. Available at: https://www.sergas.es/Asistencia-sanitaria/Estratexia-Galega-en-Enfermidades-Raras?idioma=es.

73. Department of Health - Galician Health Service. Galician Strategy on Rare Diseases. Available at: https://www.sergas.es/Asistencia-sanitaria/Estratexia-Galega-en-Enfermidades-Raras?idioma=es.

74. Community of Madrid. The Community of Madrid will update this summer its Rare Diseases Plan for the attention and care of these people. Available at:: https://www.comunidad.madrid/noticias/2023/02/27/comunidad-madrid-actualizara-este-verano-su-plan-enfermedades-poco-frecuentes-atencion-cuidado-personas.

75. Regional Ministry of Health, Regional Ministry of Education, Youth and Sports, Regional Ministry of Family and Equal Opportunities of Murcia. Plan Rare Diseases Comprehensive Plan of the Region of Murcia. Available at: https://www.carm.es/web/pagina?IDCONTENIDO=17298&IDTIPO=246&RASTRO=c890$m5859.

76. Navarra Health Service. Health Strategy for Rare or Infrequent Diseases. 2017.

77. Castilla-La Mancha Health Service. Enfermedades Raras. [accessed 6 October 2023]. Available at: https://sanidad.castillalamancha.es/ciudadanos/enfermedades-raras.

78. Osakidetza. Osakidetza Strategic Plan 2023-2025. 2023.

79. ISCIII. RPER v.24.4.6. [accessed 29 September 2023]. Available at: https://registroraras.isciii.es/Comun/Inicio.aspx.

80. BOE. Royal Decree 1091/2015 of 4 December, creating and regulating the State Register of Rare Diseases. 2015.

81. Ministry of Health, ISCIII. ReeR 2022 Report. Situation of Rare Diseases in Spain. 2022.

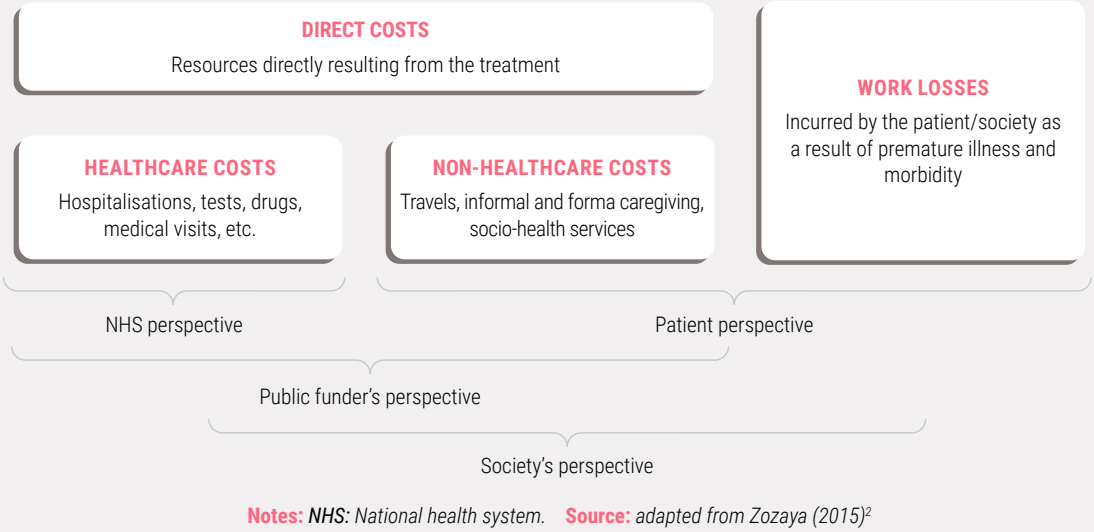
Chapter 4

The social value of orphan drugs

The social value of orphan drugs refers to the comprehensive contribution that these medicines make to society in addressing RDs in different areas. Orphan drugs contribute to improving the health outcomes of patients with rare diseases, most of which are serious, chronic and degenerative conditions for which there are no therapeutic alternatives. The use of these drugs can lead to a reduction in other costs for the health system and society, by avoiding medical visits and hospitalisations, informal care by the patient's personal environment and loss of work productivity[1,2].

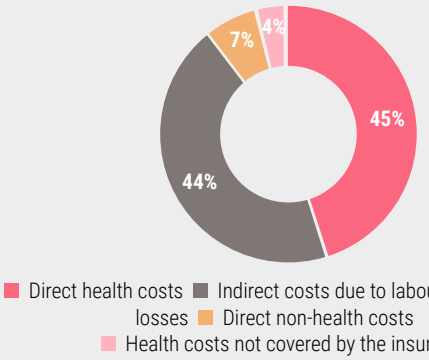
In this context, it is necessary to go beyond the simplistic focus on the budgetary impact of the medicine and to consider a comprehensive social perspective that provides an insight into the full social value of the medicine, including both direct costs and indirect costs avoided (Figure 1).

Figure 1. Type of costs included in the evaluation of medicines, depending on the perspective used



Notes: ***NHS:*** *National health system.* **Source:** *adapted from Zozaya (2015)*[2]

Figure 2. Total economic burden of rare diseases in the United States in 2019



Source: *adapted from Yang 2022*[3]

According to a US burden of disease study involving 379 RDs, 45% of the burden was attributed to the direct health care costs, followed by indirect costs (lost productivity) (44%), non-health care costs (7%) and costs not covered by insurance (4%) (Figure 2).

This chapter explores the social value of orphan drugs, highlighting relevant examples of their impact on health outcomes and patients' quality of life, as well as examples of the potential economic savings generated by the use of these medicines, providing a comprehensive view of their relevance to society.

4.1. Health outcomes and quality of life

Pharmaceutical innovation has led to unprecedented therapeutic advances in RDs, facilitating the entry of medicines for particularly severe diseases for which there are no other treatment options. These innovations have reduced mortality, delayed disease progression, alleviated symptoms and improved quality of life for patients with RDs.

The impact of OMPs on health outcomes and quality of life has been studied by several authors, both individually for specific diseases and aggregated for all available OMPs.

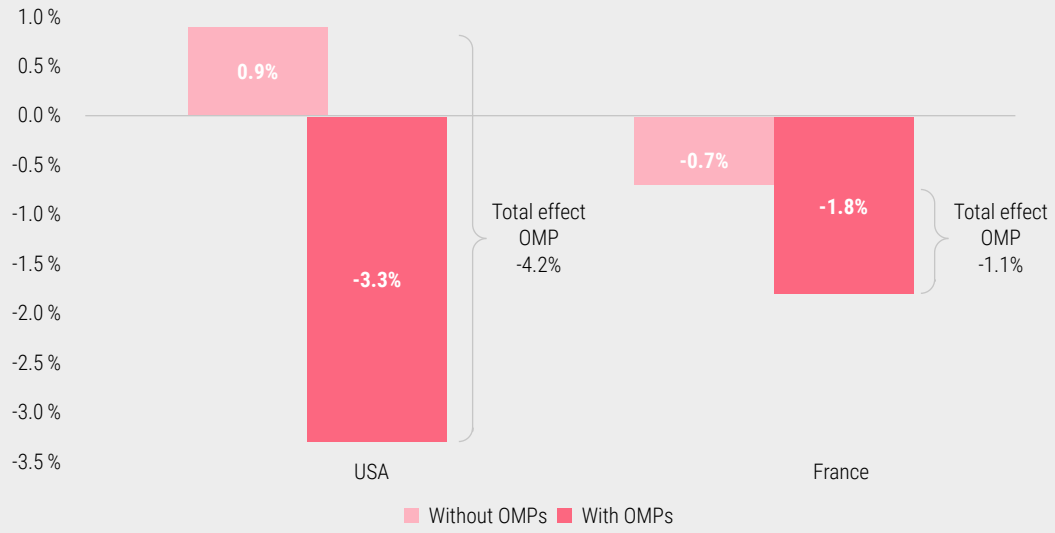
➜ Overall effect of the OMPs

Regarding the global effect of OMPs, one of the most prolific authors is the US economist Frank Lichtenberg. This author analysed, for example, the impact of the introduction of OMPs in the United States in the period between 1983 (the year in which the law promoting OMPs in the US, the Orphan Drug Act, was published) and 1999, on the mortality of people with rare diseases. The results of the study concluded that each OMP introduced prevented around 499 deaths (of which 211 were prevented in the first year) and that overall, the 216 OMPs introduced during this period prevented a total of 108,000 deaths[4].

The advent of orphan drugs during this period has helped to reduce the mortality rate for rare disease patients to below that of other diseases. (in the pre-1983 period, these mortality rates were similar)[4].

Years later, Lichtenberg analysed the effect that the increase in the number of OMPs in the US and France has had on premature mortality. The study concluded that this impact began to be seen within three years of the drug's launch and was greater in the US than in France. The study also shows that OMPs have reduced premature mortality at a faster rate than would have been the case without OMPs. In the case of France, if no OMPs had been approved between 2000 and 2007, premature mortality would have fallen by 0.7% per year. However, the approval of these drugs led to a reduction of 1.8% per year. On the other hand, premature mortality in the US would have increased by 0.9% if no OMPs had been approved, but thanks to the entry of these drugs, premature mortality decreased by 3.3% per year. Therefore, the total effect of OMPs on the growth rate of premature mortality was -4.2% in the US and -1.1% in France (Figure 3)[5].

Figure 3. Effect of approved OMPs on the annual growth rate of premature mortality, United States and France (%)



Note: *Premature mortality approximated by Potential Years of Life Lost before age 65. Period 2000-2007 for France and 1999-2006 for the USA.*

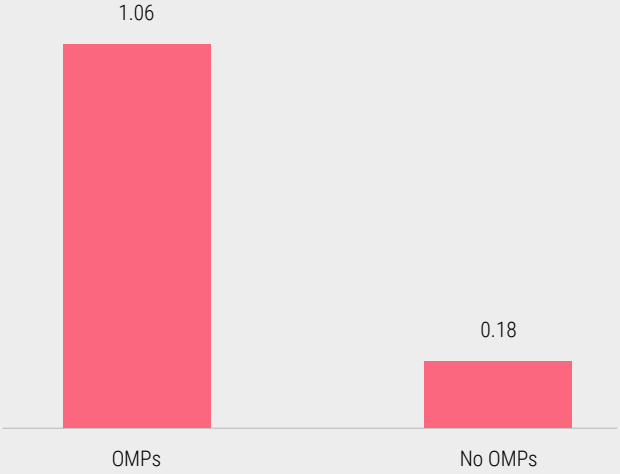
Source: *own elaboration based on Lichtenberg (2013)*[5]

Other authors have also analysed the impact of OMPs on the health of patients with RDs. For example, in 2017, a study was published comparing the improvements in quality of life achieved by 'special medicines' (indicated for diseases with a low prevalence) with those produced by traditional medicines with indications for diseases that affect a larger number of people[6]. The study concluded that the quality of life gained after the first year of the introduction of the 'special' medicine was 3-6 times greater than for traditional medicines, over the period between 1999 and 2011.

Another study, also published in 2017, analysed the impact of the European Parliament and Council regulation on OMPs. The authors concluded that between 2000 and 2017, more than 7 million European patients with RDs benefited from these medicines in terms of health, improved quality of life and reduced burden on caregivers[7].

A more recent study (2020) compared the impact of new drugs (OMPs and non-orphan drugs) with respect to previously approved therapies. The authors concluded that the new OMPs generated greater gains in Quality Adjusted Life Years (QALYs) than non-orphan drugs (average 1.06 QALYs vs. 0.18 QALYs) (Figure 4)[8].

Figure 4. Mean QALY increase compared to previous treatments, OMPs and non-OMPs



Note: ***OMP:*** *orphan medicinal product;* ***QALY:*** *quality adjusted life year.*

Source: *Chambers (2020)*[8]

➜ Particular effect of some OMPs

There are numerous examples of the impact of specific OMPs on the health of patients with certain rare diseases. Particularly noteworthy are the advanced therapies that have opened up new avenues of treatment in recent years, leading to a therapeutic revolution in the prognosis and life expectancy of rare disease patients for whom previous treatments had failed.

To facilitate the understanding of this section, it was divided into oncological and non-oncological OMPs.

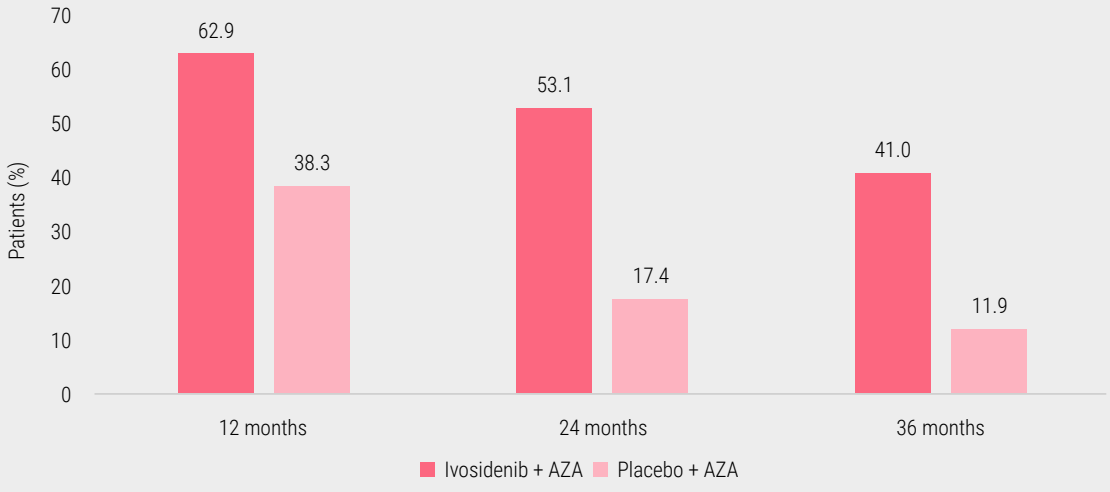
➜ Oncological OMPs

Nearly 200 rare cancers have been identified[9], accounting for 24% of new cancer diagnosed in Europe each year[10]. Among the OMPs, those targeting rare cancers represent the largest group.

Acute myeloid leukaemia (AML)

Ivosidenib therapy, applied in combination with azacitidine (IVO+AZA) is indicated for the treatment of acute myeloid leukaemia with a mutation in the IDH1 gene mutation, and has shown significant improvements over treatment with azacitidine alone. At one year, 62.9% of patients treated with IVO+AZA were alive, compared with 38.3% of patients treated with AZA alone. These results were consistent over longer follow-up periods of 24 and 36 months (Figure 5)[11].

Figure 5. Overall survival of ivosidenib+ azacitidine versus placebo+ azacitidine in the treatment of acute myeloid leukaemia.

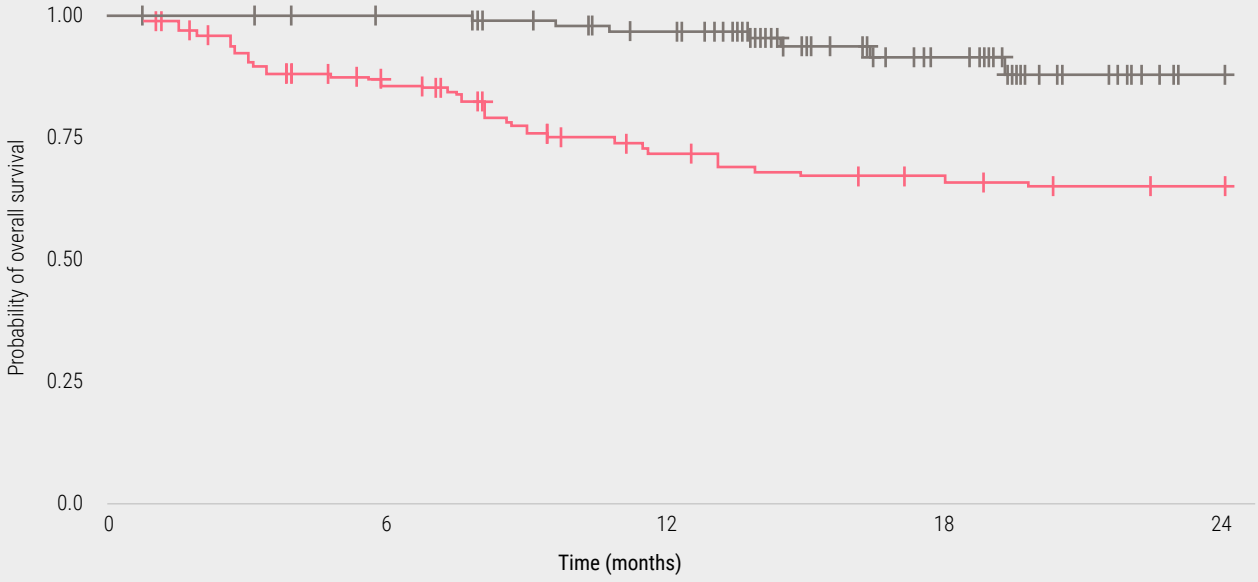


Note: ***AZA:*** *azacitidine.* **Source:** *Bhurke (2023)*[11]

Diffuse large B-cell lymphoma

One example of the radical innovation of CAR-Ts, a type of advanced therapy, is the efficacy of axicabtagene ciloleucel (axi-cel) in the treatment of diffuse B-cell lymphoma (DLBCL). Figure 6 shows how patients treated with axi-cel are more likely to survive compared to the standard of care (chemotherapy). Median overall survival was 31.0 months with axi-cel and 5.4 months with the standard treatment which suggested a 73% reduction in the risk of death with axi-cel versus standard treatment. The 2-year survival was 54% and 20% with axi-cel and standard treatment, respectively[12].

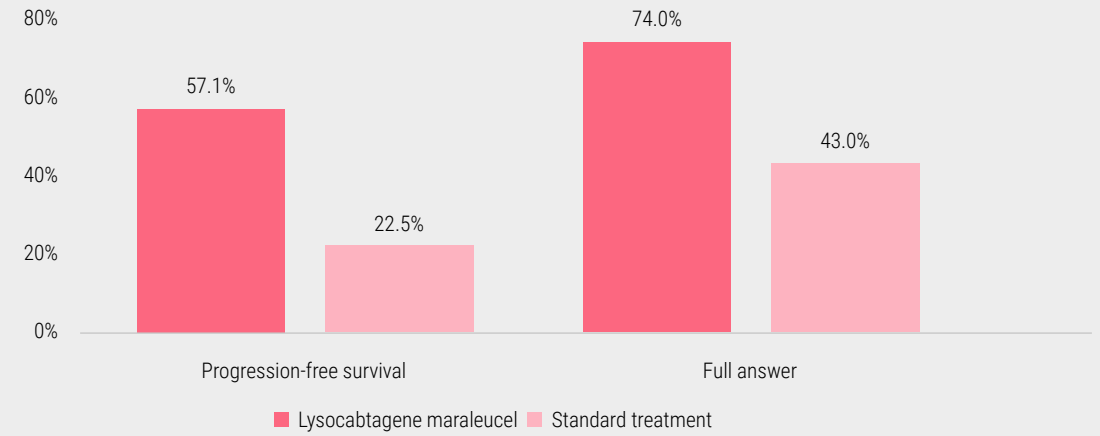
Figure 6. Overall survival with axicabtagene ciloleucel and standard salvage therapy in the treatment of diffuse large B-cell lymphoma



Source: *Neelapu (2021)*[12]

On the other hand, treatment with lysocabtagene maraleucel in DLBCL has obtained a better response than standard treatment, both in terms of progression-free survival at 12 months (57.1% vs. 22.5%) and complete response to treatment at 18 months (74.0% vs. 43.0%) (Figure 7)[13].

Figure 7. Progression-free survival and complete response in treatment of refractory or relapsed DLBCL with maraleucel lysocabtagene and standard treatment



Source: *own elaboration based on Abramson (2023)*[13]

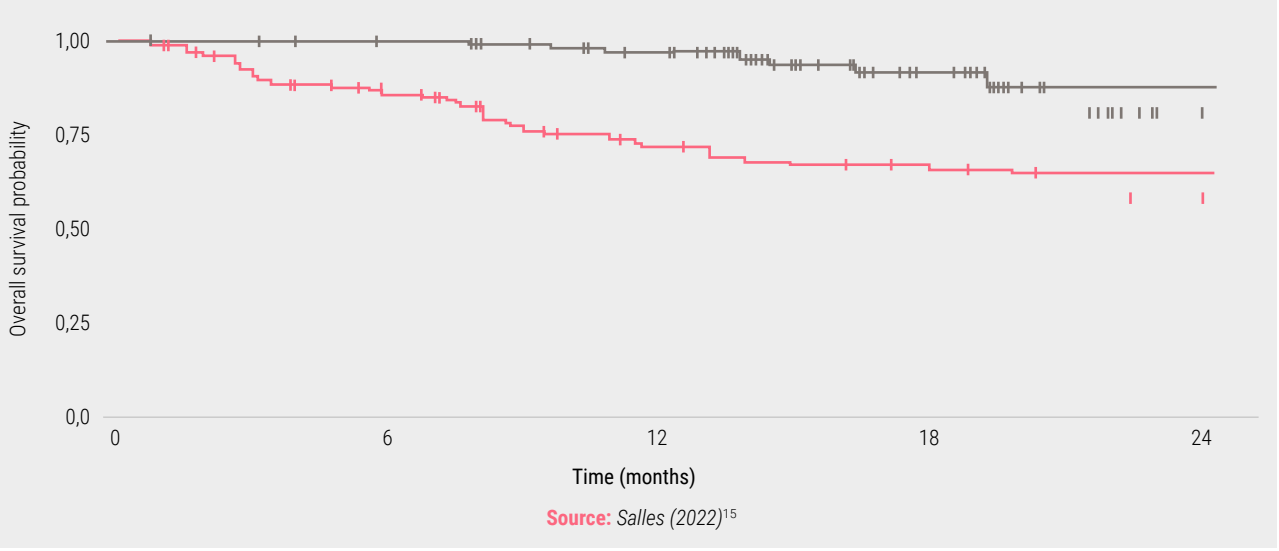
Acute lymphoblastic leukaemia

Another example of advanced therapy indicated for a rare cancer is tisagenlecleucel for the treatment of acute lymphoblastic leukaemia. Results of tisagenlecleucel in 75 patients show that overall survival was 63% at 3-year follow-up, while progression-free survival was 58% and 52% at 24 and 36 months, respectively[14].

Follicular lymphoma

Tisagenlecleucel is also indicated for the treatment of follicular lymphoma and has shown better health outcomes than standard therapy. The 12-month progression/event-free probability was 70.5% for tisagenlecleucel versus 51.9% for standard therapy. Likewise, overall survival at 12 months was 96.6% versus 71.7% in the tisagenlecleucel and standard treatment groups, respectively (Figure 8)[15].

Figure 8. Progression-free survival in follicular lymphoma treatment with tisagenlecleucel (Elara) versus treatment as usual (reCORD-FL)



Source: *Salles (2022)*[15]

Uveal melanoma

The launch of tebentasfusp therapy in 2022 for the treatment of advanced uveal melanoma, a rare eye cancer for which there was no standard treatment is another example of how OMPs can considerably improve health outcomes of patients with RDs. The tebentasfusp clinical trial showed that patients treated with tebentasfusp survived an average of 21.7 months, compared to 16.0 months for patients receiving a comparator[16,17].

➜ Non-oncological OMPs

There are also several recent examples in the scientific literature of the positive impact of specific orphan drugs on the health outcomes of patients with rare non-oncological diseases, as detailed below.

Severe veno-occlusive disease of the liver

Defibrotide for severe veno-occlusive liver disease has been shown to improve patients' complete response (23.5% of those treated in the trial vs 9.4% in the historical control) and survival rate (38.2% vs 25% of the historical control)[18].

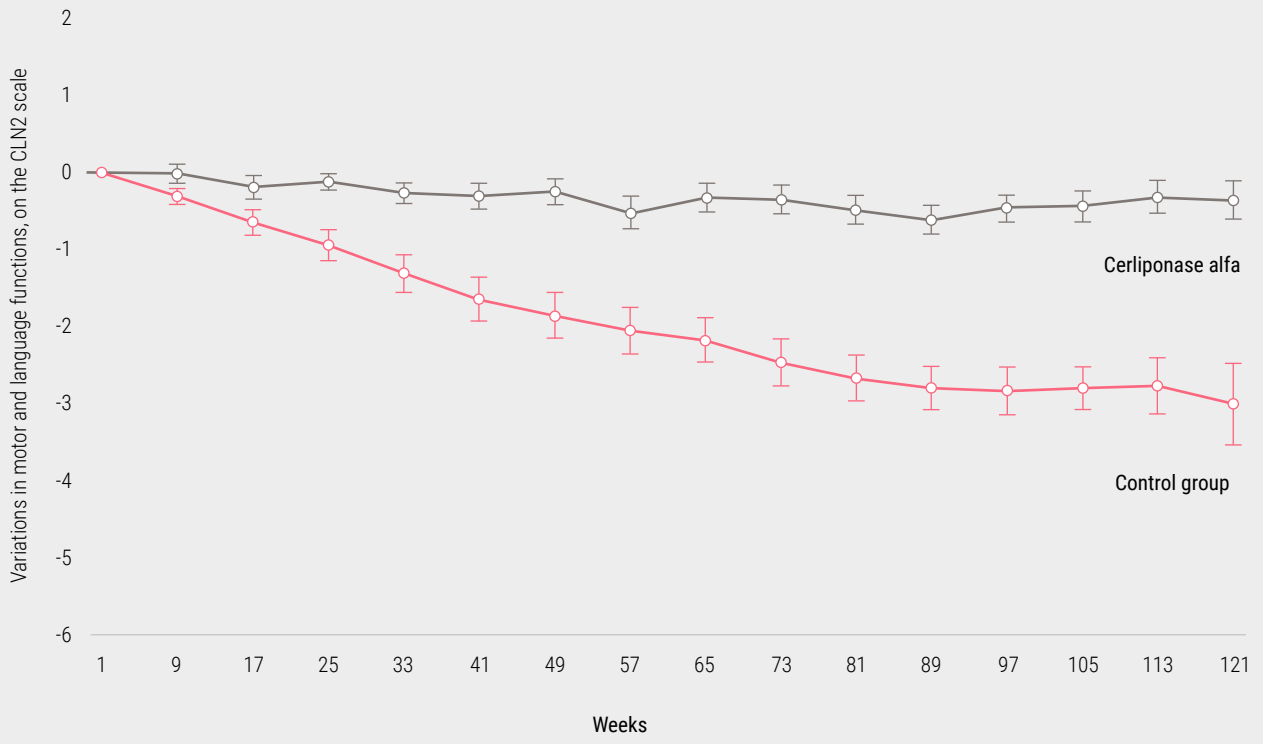
Lysosomal acid lipase deficiency

Similarly, sebelipase alfa therapy, the first treatment for lysosomal acid lipase deficiency, introduced in 2015, reduced multiple liver (70% better alanine aminotransferase level normalisation rates versus placebo) and lipid abnormalities (56% and 78% better results in triglyceride and cholesterol levels, respectively, versus placebo) related to this potentially lethal condition in children and adults[19].

CLN2 disease

CLN2 is a rare disease that causes progressive neurological deterioration in children, including seizures, personality disorders, dementia and loss of the ability to walk, speak and communicate. In a study of 24 children aged 3 to 16 years, the effect of intraventricular infusion of cerliponase alfa every 2 weeks for 96 weeks was evaluated, concluding that the rates of motor and language impairment were significantly lower in patients on this treatment than in the control group (-0.2 vs -1.9 at week 49; -0.5 vs -2.8 at week 97) (Figure 9)[20].

Figure 9. Impact of cerliponase alfa treatment on motor and language functions in children aged 3-16 years with CLN2. Germany, England, United States and Italy, variations on the CLN2 scale

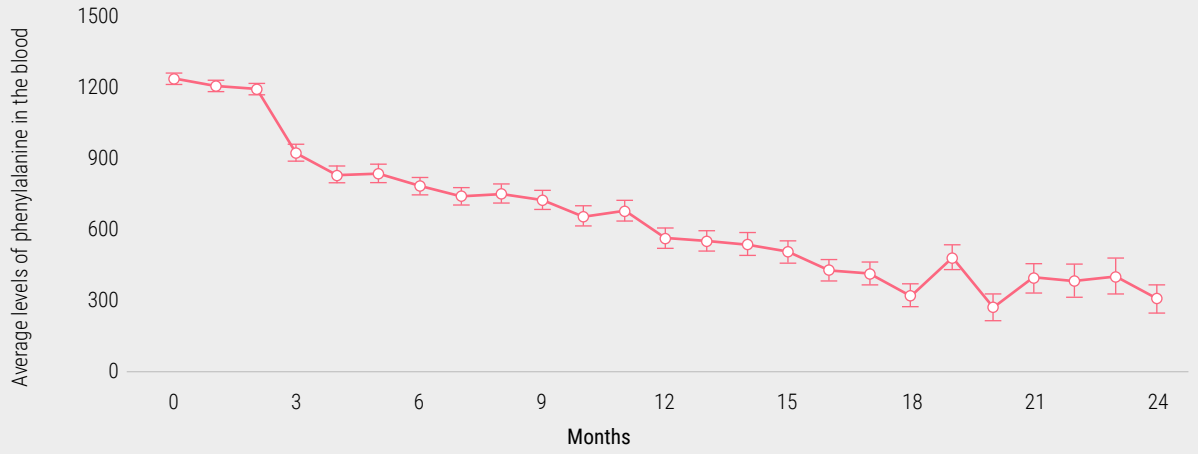


Note: ***CLN2:*** *Ceroid Neuronal Lipofuscinosis Type 2.*
Source: *Schulz (2018)*[20]

Phenylketonuria

Phenylketonuria (PKU) is a disease caused by phenylalanine hydroxylase deficiency, leading to high concentrations of phenylalanine in the blood, impairing brain function and development. The approval of pegvalyase, a novel enzyme therapy, represents a major breakthrough as it responds to an unmet need with existing treatments. The efficacy of this treatment has been demonstrated in a study of 261 adult patients. Compared to the initial period, after 1 and 2 years, pegvalyase treatment showed a 54% to 75% reduction in blood phenylalanine levels (1,232 µmol/L at baseline versus 564.5 and 311.4 after 1 and 2 years, respectively) (Figure10)[21].

Figure 10. Effect of pegvalyase use versus baseline treatment status. Mean blood phenylalanine levels in adult PKU patients after 1 and 2 years, United States



Nota: ***PKU:*** *genetic disorder called phenylketonuria.*

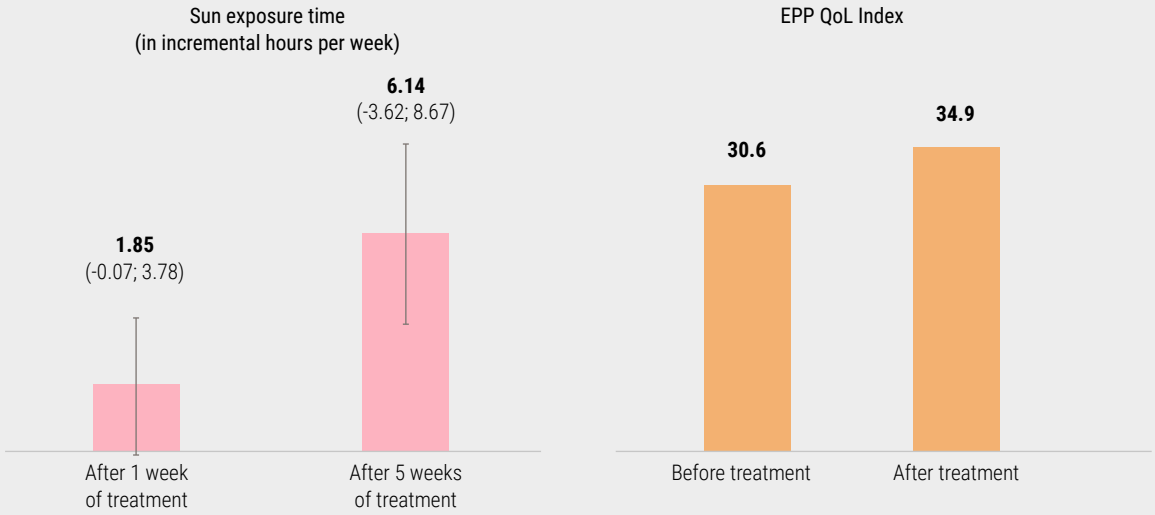
Source: *Thomas (2018)*[21]

Erythropoietic photoporphyria

Patients with light sensitivity caused by erythropoietic photoporphyria (EPP) can experience significant deterioration in their quality of life, as brief exposure to the sun can cause extremely painful skin lesions. The use of afamela- notide allows these patients to spend more time exposed to the sun, and consequently an improvement in their quality of life.

This has been demonstrated in a study of 117 people in the Netherlands where, following afamelanotide use, there an increase of 6.1 hours per week in the time these patients were able to spend in sunlight exposure (95%CI 3.62 to 8.67, p<0.01) and a 14% increase in the quality-of-life index (95%CI 4.53% to 23.50%) (Figure 11)[22].

Figure 11. Impact of afamelanotide use in patients with EPP on sun exposure time and quality of life after 5 weeks, Netherlands



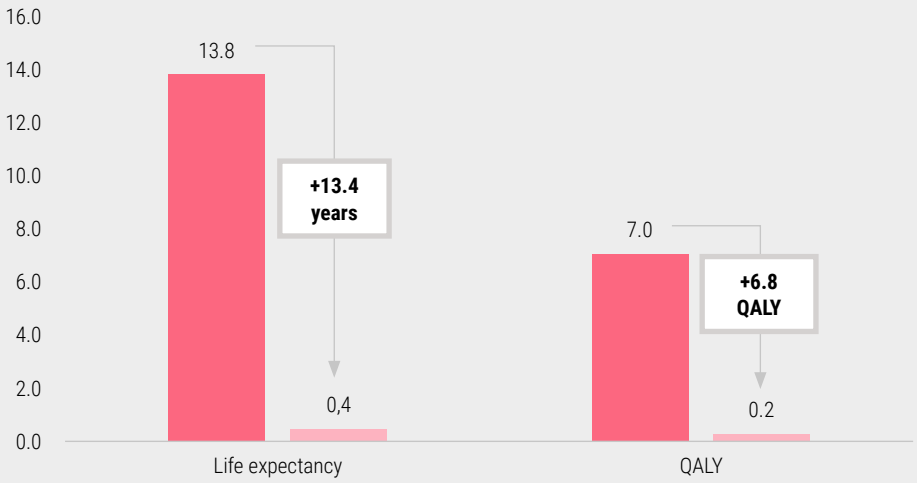
Note: ***EPP:*** *Erythropoietic photoporphyria.* ***QoL:*** *Quality of Life Questionnaire for erythropoietic photoporphyria disease.*

Source: *own elaboration based on Wensink (2020)*[22]

Pompe disease

Pompe disease is a rare infantile metabolic disease that causes respiratory and feeding problems, respiratory tract infections and generalised muscle weakness. Patients also show progressive thickening of the heart that eventually leads to heart failure, leading to death before the first year of life. However, alglucosidase alfa has shown significant improvements over the historical record of untreated patients. It has been shown to increase life expectancy by 13.4 years compared to standard treatment (13.8 versus 0.4) as well as an improvement in QALYs of 6.8 years (7.0 versus 0.2). In addition, the study also shows that 65% of children are still alive after 5 years, with no deaths observed thereafter (Figure 12)[23].

Figure 12. Difference in life expectancy and QALYs in alglucosidase alfa therapy versus standard treatment in Pompe disease

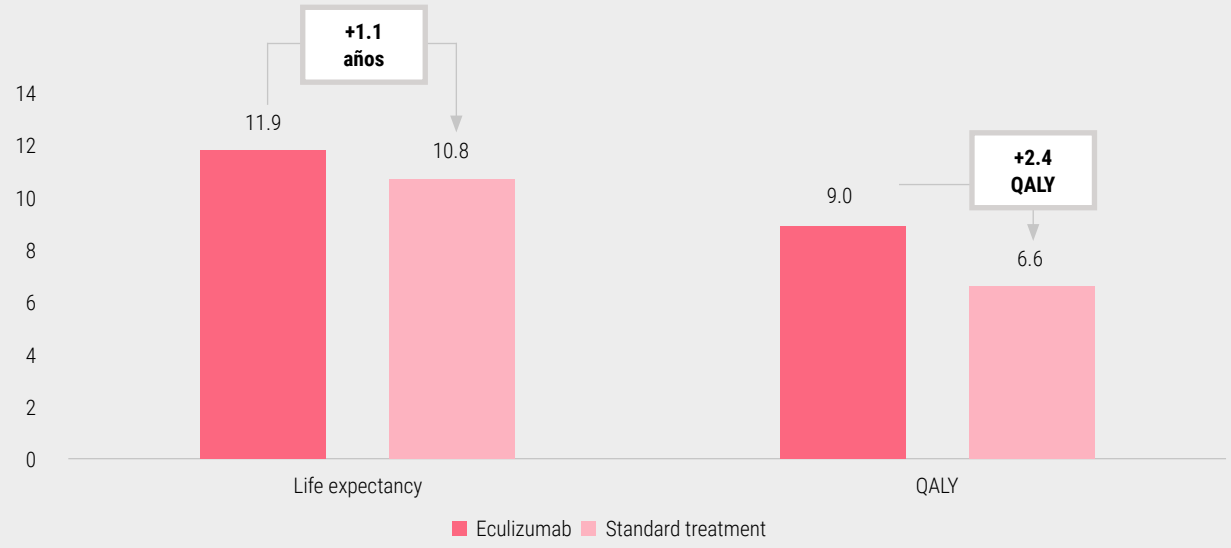


Source: *Kanters (2014)*[23]

Paroxysmal nocturnal haemoglobinuria

Another example where a new treatment offers better health outcomes than standard practice is seen in paroxysmal nocturnal haemoglobinuria (PNH), a rare disease that causes red blood cells to disintegrate[24]. The median survival of PNH from diagnosis is 14.6 years, with thrombosis and renal failure accounting for 60% of all deaths. Eculizumab has been shown to improve the quality of life of patients with PNH, achieving 2.4 more QALYs than standard treatment, as well as increasing patient life expectancy by 1.1 years (Figure 13)[25].

Figure 13. Difference in life expectancy and QALYs in eculizumab therapy versus usual treatment in paroxysmal nocturnal haemoglobinuria, Canada

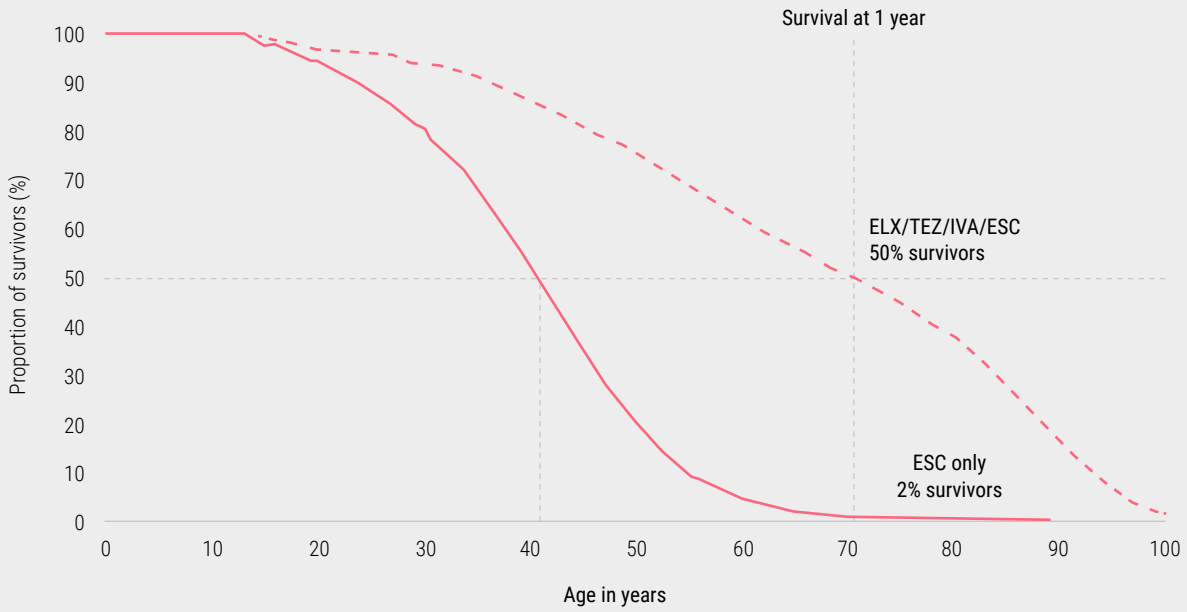


Source: *Coyle (2014)*[25]

Cystic fibrosis

The combination therapy of elexacaftor/tezacaftor/ivacaftor together with supportive therapy (clearance, bronchodilators, mucolytics, antibiotics and nutritional management) to treat cystic fibrosis increase the median survival of cystic fibrosis patients by 29.7 years (70.4 years vs. 40.8 years), compared to supportive therapy (Figure 14)[26], which is a radical change in clinical practice.

Figure 14. Impact of elexacaftor/tezacaftor/ivacaftor therapy on cystic fibrosis treatment



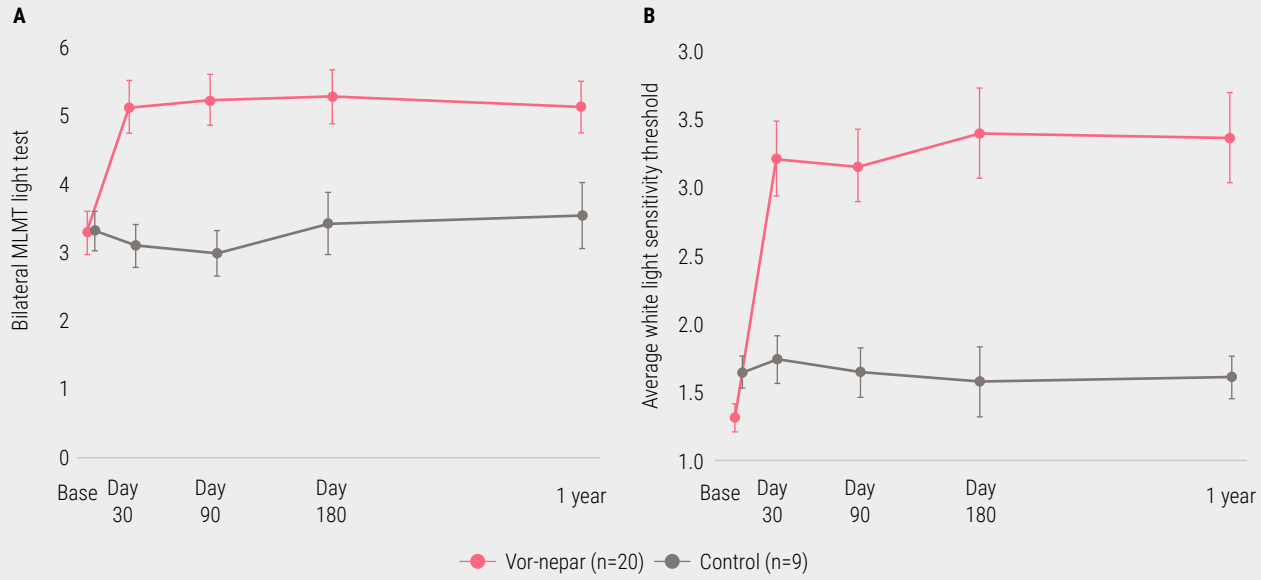
Note: ***ELX/TEZ/IVA:*** *elexacaftor/tezacaftor/ivacaftor;* ***ESC:*** *Enhanced supportive care (airway clearance, bronchodilators, mucolytics, antibiotics and nutritional management).*

Source: *adapted from Rubin (2022)*[26]

Hereditary retinal dystrophy

Advanced therapies have also provided new and more effective treatments in the field of non-oncological RDs. One example is voretigén neparvovec therapy for hereditary retinal dystrophy, a rare disease that causes night vision loss, progressive loss of the peripheral visual field and blindness. After one year, patients treated with voretigene neparvovec performed better on the bilateral light test, achieving a 1.8-point improvement compared to a 0.2-point improvement in the control group (Figure 15A). Voretigene neparvovec also achieved improvements over the control group in other tests, such as the white light sensitivity test. In this case, the control group showed no improvement from the start of the study meanwhile after one year, there was a difference of 2.11 points between patients treated with voretigén neparvovec and the control group (Figure 15B)[27].

Figure 15. Mean change in bilateral MLMT light test A) and white light sensitivity (B) in hereditary retinal dystrophy treatment with voretigene neparvovec versus control group



Note: ***MLMT:*** *bilateral multi-luminescent mobility test;* ***Vor-nepar:*** *voretigene neparvovec*

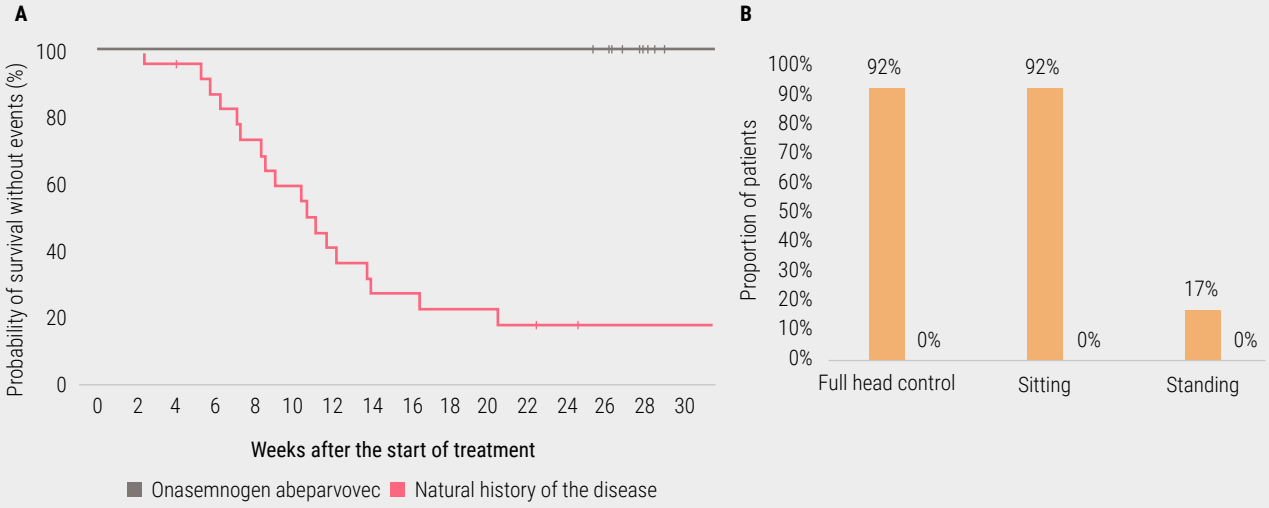
Source: *Rusell (2017)*[27]

Spinal muscular atrophy

The first drug indicated for spinal muscular atrophy (nusinersen), introduced in 2013, has been shown to improve both overall survival and motor function in patients participating in clinical trials, reducing the risk of death or permanent ventilation by 47% compared to the placebo group[28].

In addition, an advanced therapy (onasemnogen abeparvovec) has been developed that has demonstrated improvements in both survival (Figure 16A) and motor milestone achievement (Figure 16B). Of the 12 infants who received the proposed therapeutic dose, 11 were able to sit independently and two were able to stand and walk independently at the final 24 months post-treatment visit. After completion of the study, two more patients achieved independent sitting and two more patients achieved supported standing after enrolment in the long-term follow-up study[29].

Figure 16. Effectiveness of onasemnogen abeparvovec vs the natural history of the disease in the treatment of SMA



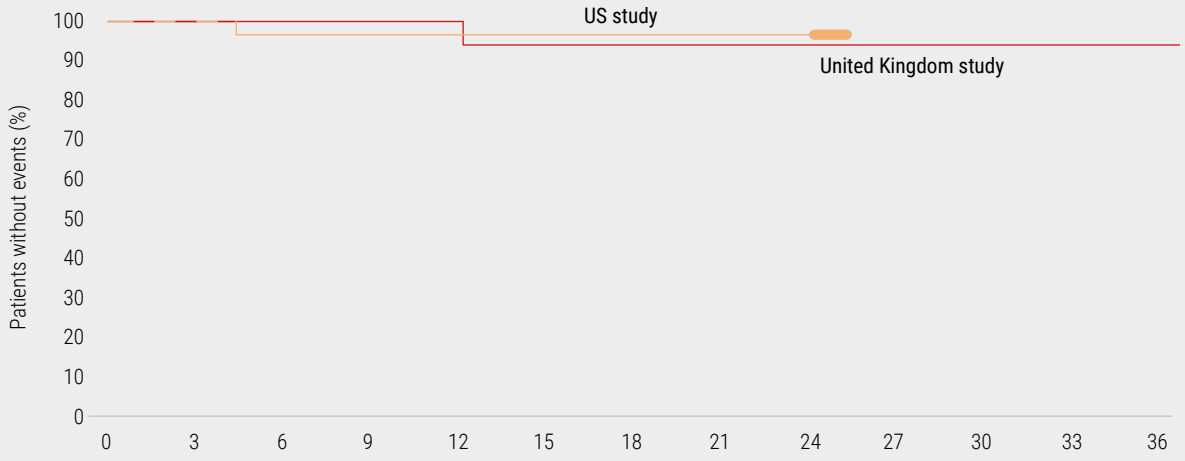
Note: ***A:*** *Probability of event-free survival in children who received onasemnogene abeparvovec versus natural history data.* ***B:*** *Motor milestones reached by children treated with onasemnogene abeparvovec versus natural history data of the disease*

Source: *adapted from Al-Zaidy (2019)*[29]

ADA-SCID

In another rare and serious condition called ADA-SCID, the advent of an innovative drug that modifies patients' CD34+ cells has led to promising results for patients with ADA-SCID. ADA-SCID is a rare disease that affects the immune system, causing recurrent fungal, bacterial and viral infections and growth problems. Without treatment, children rarely survive more than 2 years. To manufacture this drug, stem cells from the child's bone marrow are modified in the laboratory by inserting a gene that produces the enzyme that the patient does not naturally produce. In a study of two different populations (in the UK and the US), patients treated with the innovative drug achieved 100% overall survival in both groups at 24 and 36 months. Event-free survival was 97% (US group) and 100% (UK group) at 12 months and 97% and 95% at 24 months, respectively (Figure 17)[30].

Figure 17. Percentage of event-free patients in the treatment of severe combined immunodeficiency syndrome due to adenosine deaminase deficiency with the autologous cell fraction enriched with CD34+ cells, United States and United Kingdom

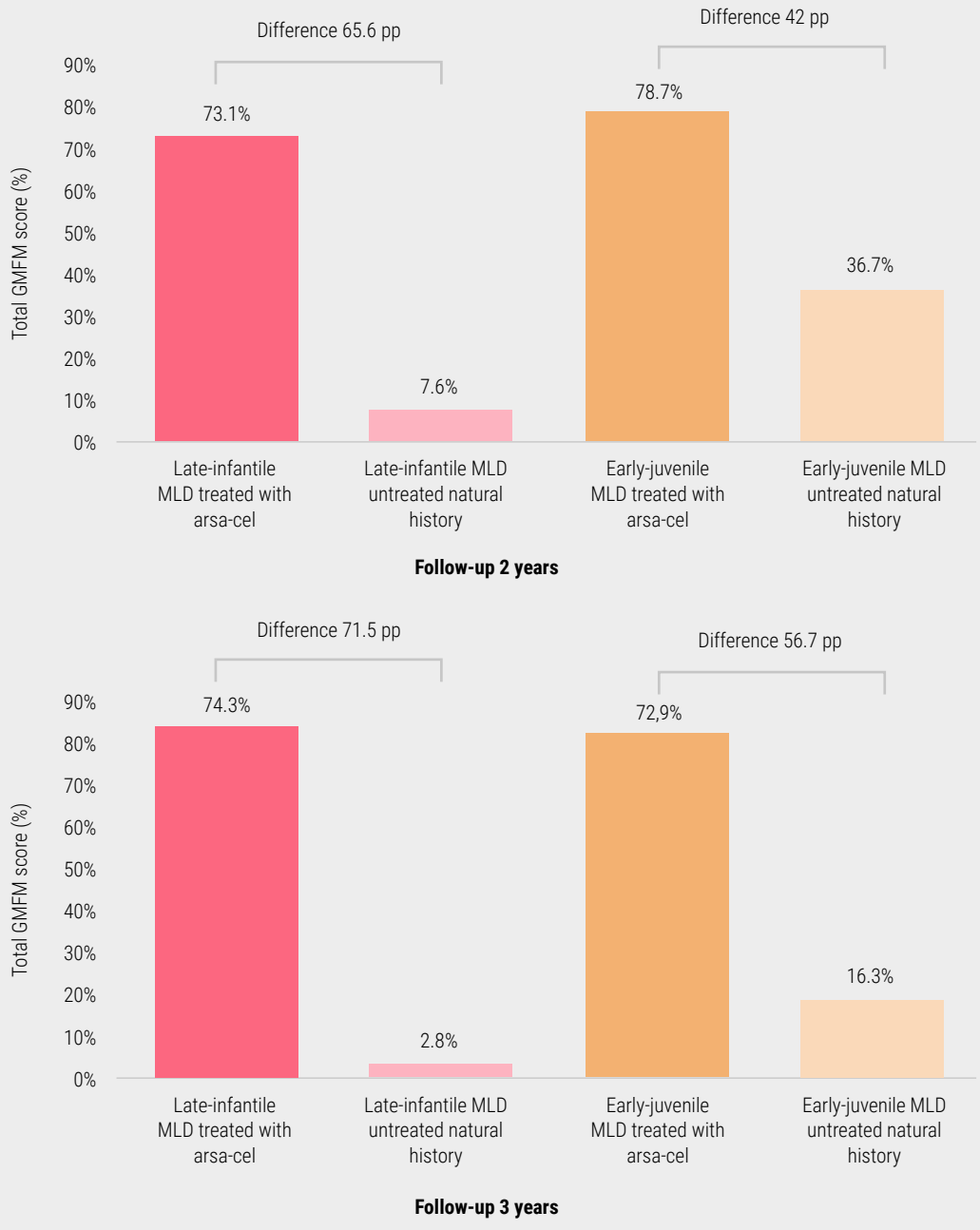


Source: *Kohn (2021)*[30]

Metachromatic leukodystrophy

Another advanced therapy in the rare diseases are is atidarsagen autotemcel, which was authorised for the treatment of childhood metachromatic leukodystrophy (MLD). MLD is a rare inherited disease that causes symptoms such as difficulty walking, gradual mental deterioration and death. Atidarsagen autotemcel has been shown to be effective, achieving differences of up to 71.5 percentage points on the developmental motor function test (GMFM) compared to a cohort of untreated patients, who followed the natural history of the disease, at 3-year follow-up (Figure 18)[31].

Figure 18. GMFM scores for patients with late-infantile and early-juvenile MLD treated with atidarsagene autotemcel atidarsagen versus natural history of disease, Italy



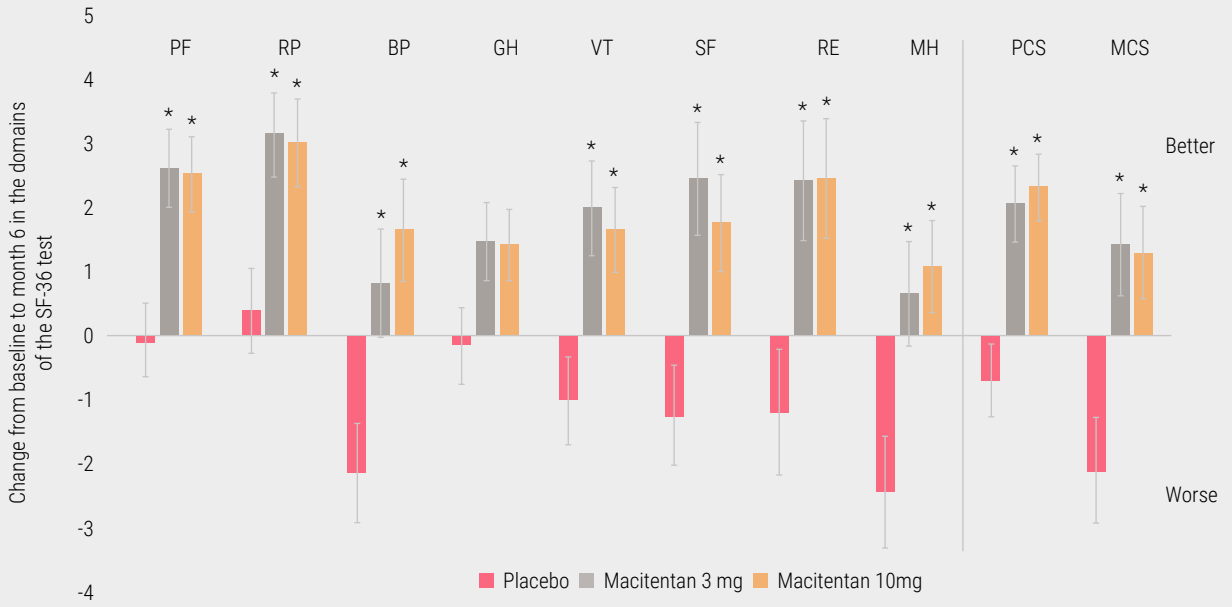
Note: ***GMFM:*** *The Gross Motor Function Measure;* ***MLD:*** *metachromatic leukodystrophy;* ***pp:*** *percentage points.*

Source: *Fumagalli (2022)*[31]

Pulmonary arterial hypertension

In the case of pulmonary arterial hypertension, macitentan therapy has been shown not only to improve patients' health status, but also their quality of life. Using the SF-36 questionnaire, treatment with macitentan 10 mg significantly improved seven of the eight domains of the SF-36 compared to placebo. Significant improvements were also shown in seven of eight individual domains of the SF-36 and in SCF and SCM scores after treatment with macitentan 3 mg compared to placebo (Figure 19)[32].

Figure 19. Quality of life measures using the SF-36 questionnaire with placebo, macitentan 3 mg or macitentan 10 mg in the treatment of PAH



Note: ***BP:*** *bodily pain;* ***GH:*** *general health;* ***MCS:*** *mental component summary;* ***MH:*** *mental health;* ***PCS:*** *physical component summary;* ***PF:*** *physical functioning;* ***RE:*** *role-emotional;* ***RP:*** *role-physical;* ***SF:*** *social functioning;* ***VT:*** *vitality.*

Source: *Mehta (2017)*[32]

4.2. Cost savings

The burden of RDs is significant in many ways, affecting patients, their families and society as a whole. In addition to the clinical impact, there are economic costs to health care systems and to the patients and their emotional environment. The emotional burden and reduced quality of life of those affected is exacerbated by the lack of specific treatments, while health systems are under pressure to manage complex and rare conditions.

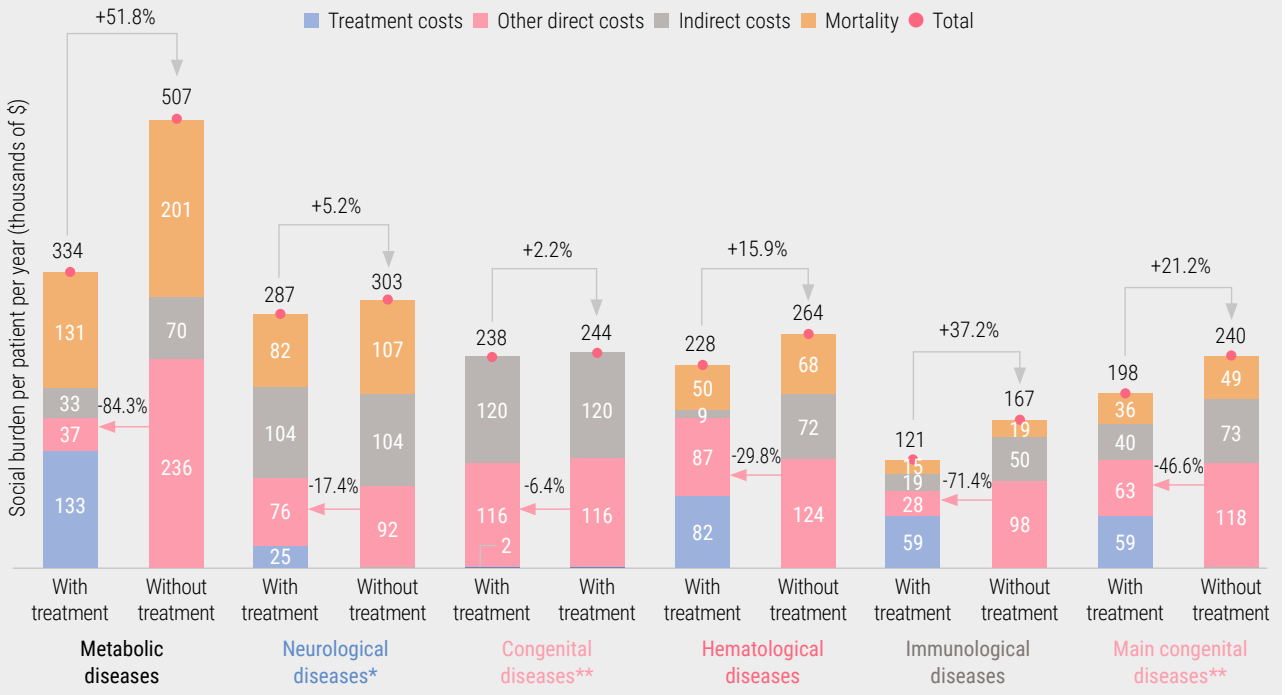
However, the introduction of targeted treatments for these conditions represents a tangible hope for alleviating this burden. These treatments not only aim to improve patients' quality of life but can also have a significant impact on the associated economic burden. As we move forward in this section, we will explore how the implementation of targeted therapies can not only mitigate the direct healthcare costs associated with medical treatment and care but also reduce the costs care provided by the patient's environment and the indirect costs linked to lost work productivity and other factors associated with these rare diseases.

In a US study, they used an economic tool to analyse the impact of existing treatments in priority therapeutic areas, such as rare metabolic, neurological, congenital, haematological and immunological diseases, covering a total of 227 well-documented rare metabolic, neurological, congenital, haematological and immunological diseases. From this, the 24 most relevant RDs were selected based on criteria such as unmet need, relative importance for patients, scientific interest, prevalence and apparent burden of disease. Finally, the direct, indirect and mortality-related costs of these 24 RDs were assessed to compare the burden of care with and without

treatment. In the analysis, direct costs comprised the cost of treatment, medical procedures, hospitalisations, medical visits, home health care and other medical costs. Indirect costs were based on loss of patient and caregiver productivity, loss of work, changes in the home, cost of secondary treatments, travel expenses and accommodation for medical visits[33].

The results showed that the economic burden of the most important RDs is mainly driven by direct costs and mortality-related costs, with metabolic and neurological diseases having the highest overall burden. Eliminating the treatment resulted in a 2.2% increase for congenital diseases and 51.8% for metabolic diseases. Therefore, introducing a specific treatment for a rare disease can significantly reduce direct costs, especially in metabolic diseases, where a reduction of more than 80% in direct costs has been recorded when a treatment is introduced. Similarly, specific treatment for immunological diseases is able to reduce direct costs by more than 70% (Figure 20).

Figure 20. Assessment of the value of the burden of disease and other annual costs per patient for rare diseases, with and without treatment (24 rare diseases), United States



Notes: *The bars represent the average burden per person per year (broken down by cost driver) associated with the therapeutic areas, as well as the average for selected diseases across all therapeutic areas. *Spinal muscular atrophy is excluded because it was an outlier in this area. **Of the main diseases selected in the congenital therapeutic area, Christianson and Delection 5P were excluded because there is no treatment for these diseases, therefore there is no difference in the magnitude of the costs.*

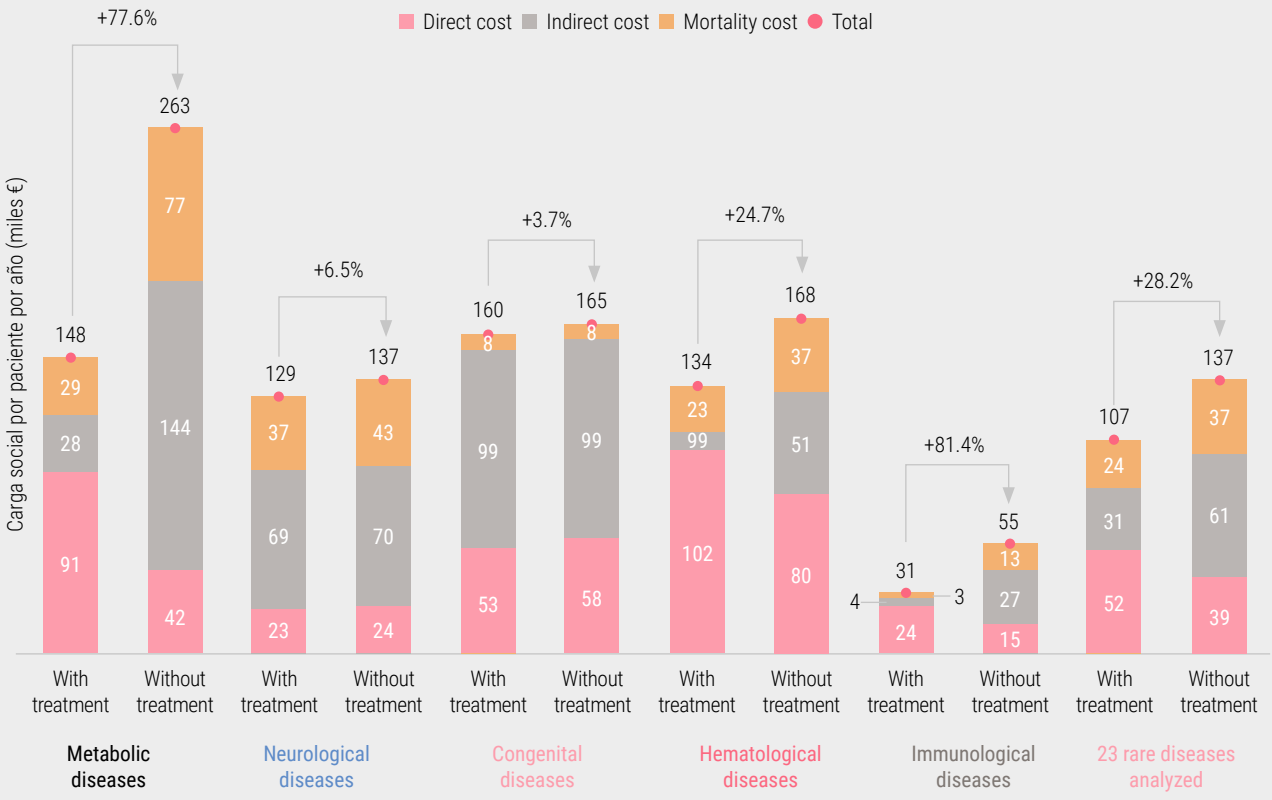
Source: *adapted from Andreu (2022)*[33]

Furthermore, although indirect costs generated by RDs are significant, treatments can reduce labour productivity losses. This is particularly true for haematological and immunological diseases, where specific treatments can reduce the associated indirect costs by 87.5% and 60% respectively.

Although therapies reduce the burden of RD, the economic burden remains high even when specific therapies exist. Moreover, when pharmacotherapy is introduced, the composition of costs changes, as there is a reduction in direct health care costs, which can be transferred to indirect costs. These findings support the idea that the development of safe and effective treatments for RDs generates significant social value[33].

These results are in line with a similar study conducted by the same author, but at the European level, where it was reported that, in a no-treatment scenario, the total burden per patient per year would increase by 28% for the 23 RDs included in the analysis[34]. For metabolic diseases, the untreated burden would increase significantly (77.6%), mainly due to reduced life expectancy without enzyme replacement therapies and the possible need for ongoing mental health care for patients with phenylketonuria. For immunological disorders, the untreated burden would increase by 81.4%, partly due to reduced mortality from OMPs. In haematological diseases, in the absence of treatment, the increase in burden would be 24.7%, as patients would require additional care and have more absenteeism from work, resulting in a higher loss of productivity. In congenital diseases, there are no disease-modifying therapeutic options, only basic treatments to control specific symptoms, so the increase in burden without treatment would be the lowest among the most relevant therapeutic areas of RDs. Finally, in neurological diseases, the burden would increase by 6.5%, mainly due to accelerated neurodegeneration and the need for increased medical care and hospitalisations for untreated patients (Figure 21).

Figure 21. Assessment of the value of the burden of disease per patient per year in treated and untreated rare diseases (23 rare diseases), Germany-France-Italy



Note: *direct costs include the cost of treatment, although not in a disaggregated way that allows separation of the cost.*

Source: *adapted from Andreu (2023)*[34]

Again, these findings also demonstrate that targeted treatments could reduce the indirect costs associated with certain rare diseases by up to 80%. This is particularly true for metabolic, haematological and immunological disease. It was also concluded that the existence of treatments not only has a positive value in terms of a lower financial burden on families and healthcare systems but also as a critical factor in avoiding an overall increase of 28% in the economic burden per rare disease patient per year in the scenario of no therapeutic options.

➜ Direct costs

Direct costs associated with diseases are a critical aspect of resource management in health care and are particularly relevant in the field of OMPs. In this case, direct cost savings refer to the ability of RDs treatments to reduce the costs of medical visits, hospitalisations and treatments covered by the NHS, as well as other health and social services required by these patients, while seeking to improve their health and quality of life.

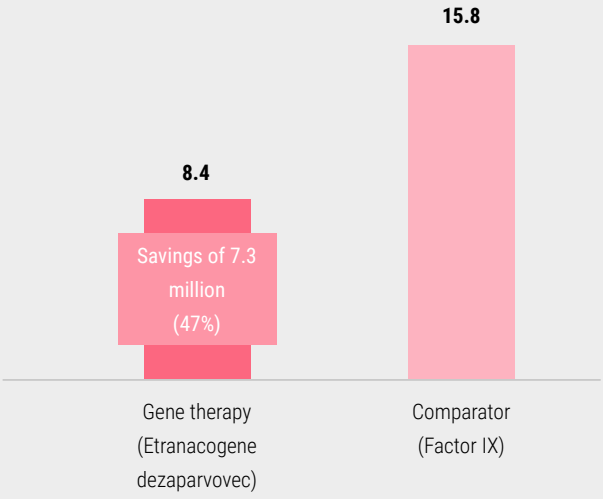
Despite its initial incremental costs, the use of ODs is often offset by a reduction in other direct healthcare costs. Below are some examples of how the use of ODs can generate economic savings for healthcare systems.

Haemophilia

According to an analysis conducted by the Institute for Clinical & Economic Review (ICER), gene therapies have been shown to generate significant economic savings in the field of haemophilia B, while offering improved patient health outcomes and becoming the best option compared to their alternatives (Figure 22)[35].

Treatment with etranacogene dezaparvovec gene therapy would be associated with a cost of $8.4 (including $953,000 in non-drug costs) over lifetime, as opposed to the $15.8 million associated with weekly factor IX treatment (a savings of $7.3 million, equivalent to 47%). This therapeutic approach also translates into improvements in QALYs, with a value of 17.98 compared to 17.31, and a reduction in the total number of bleeding episodes (182 with gene therapy vs. 247 with the comparator), which would make it the dominant choice[35].

Figure 22. Direct lifetime costs per haemophilia patient treated with gene therapies vs. comparators, in millions of dollars



Source: *own elaboration adapted from Tice (2022)*[35]

It should also be noted that primary prophylaxis is the emerging standard treatment for children with severe haemophilia and it has been shown that tailored prophylaxis (dose-escalation), which starts at a low frequency and increases with repeated bleeds, can prevent arthropathy at a lower cost than standard prophylaxis. Specifically, tailored dose-escalated prophylaxis has an additional cost of $3,192 per joint bleed prevented, while standard prophylaxis has an additional cost of $9,046 per joint bleed prevented compared to dose-escalated prophylaxis. Therefore, the savings from using tailored dose-escalated prophylaxis compared to the standard prophylactic regimen would be $5,854 per joint haemorrhage avoided[36].

Cystic fibrosis

En the field of cystic fibrosis (CF), elexacaftor/tezacaftor/ivacaftor stands out as a highly effective modulator of the cystic fibrosis transmembrane conductance receptor (CFTR), generating notable clinical benefits such as increased FEV1[I], reduced sweat chloride and reduced pulmonary exacerbations in CF patients[37].

A retrospective study conducted at the Kaiser Permanente CF Clinic, which included 31 patients, evaluated hospitalisation costs in the 3 years prior to the introduction of this drug in 2020. These costs were compared with those incurred in 2020. Since the introduction of elexacaftor/tezacaftor/ivacaftor, no patient has required hospitalisation, resulting in no hospital costs, whereas in the years prior to treatment, annual hospital costs amounted to $2.5 million. In other words, 100% savings were achieved in this cost category, amounting to $2.5 million per year[37]. These savings played a significant role in offsetting drug costs and were most pronounced in patients with severe lung disease (12 of the 31 patients studied), who accounted for 80% of all hospital costs. In this subgroup, savings in hospital costs offset 75% of drug expenditure[37].

I ***FEV1:*** *Forced expiratory volume in the first second. It is a parameter used in pulmonary function tests to measure the amount of air a person can exhale in the first second of a forced exhalation after a deep inhalation. The FEV1 value is expressed in litres or as a percentage of total lung volume and provides information on airway obstruction and severity of lung disease.*

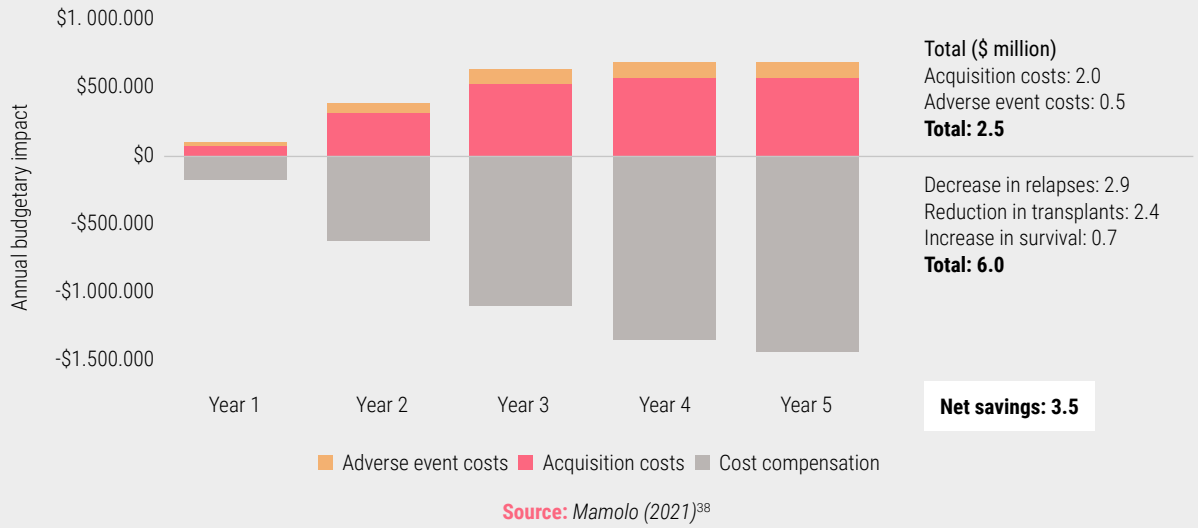
Acute myeloid leukaemia

Gemtuzumab ozogamicin (GO) is used for the treatment of adults with newly diagnosed CD33-positive (CD33+) acute myeloid leukaemia, as well as adult and paediatric patients with relapsed/refractory (R/R) and CD33-positive (CD33+) AML[38].

In the United States, economic modelling was used to estimate the budgetary impact of introducing GO in combination with chemotherapy versus using chemotherapy over a 5-year period in a health plan with one million members[38].

Over the period studied, a total of $2.5 million in acquisition and adverse event costs were estimated. However, the benefits related to fewer relapses, fewer transplants and longer survival were estimated at $6.0 million (2.9, 2.4 and 0.7, respectively), representing a total saving of 2.4 times the acquisition and adverse event costs (Figure 23)[38].

Figure 23. Net annual budget impact of adding gemtuzumab ozogamicin for newly diagnosed acute myeloid leukaemia in combination with standard chemotherapy, US



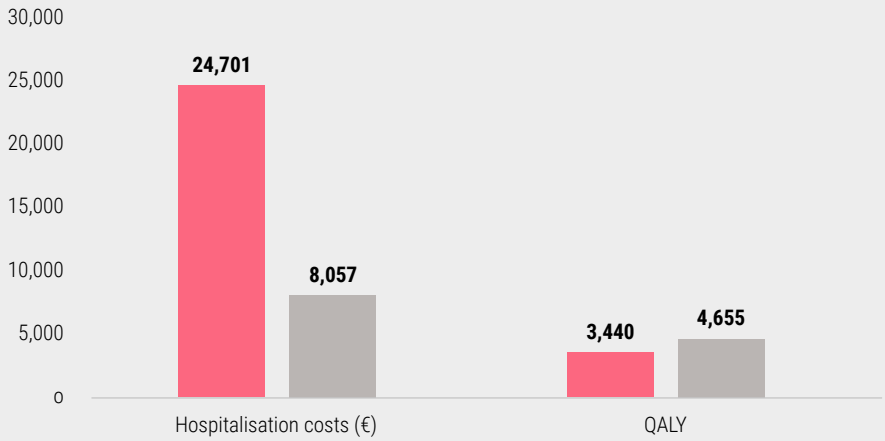
Source: *Mamolo (2021)*[38]

Veno-occlusive disease

Veno-occlusive disease (VOD) is an unpredictable condition that represents one of the leading causes of mortality following haematopoietic cell transplantation. Without treatment, patients with severe VOD can die within days or weeks after transplantation[39]. Defibrotide is indicated for the treatment of severe VOD, also known as sinusoidal obstructive syndrome (SOS) in haematopoietic progenitor cell transplantation[39].

The hospitalisation costs and health outcomes associated with the introduction of defibrotide compared to usual care (supportive care) were evaluated in Spain over a one-year period, using a Markov model. The incorporation of this drug would result in 67% reductions in hospitalisation costs (€8,057 per patient treated with defibrotide versus €24,701 with usual care) and 35% improvements in quality of life (defibrotide: 4,655 QALYs; usual care: 3,440). These savings in hospitalisations would offset the cost of drug acquisition by 33% (Figure 24)[39].

Figure 24. Hospitalisation costs and health outcomes associated with the use of fibrotide compared to usual care in the treatment of severe veno-occlusive disease in Spain, 1 year



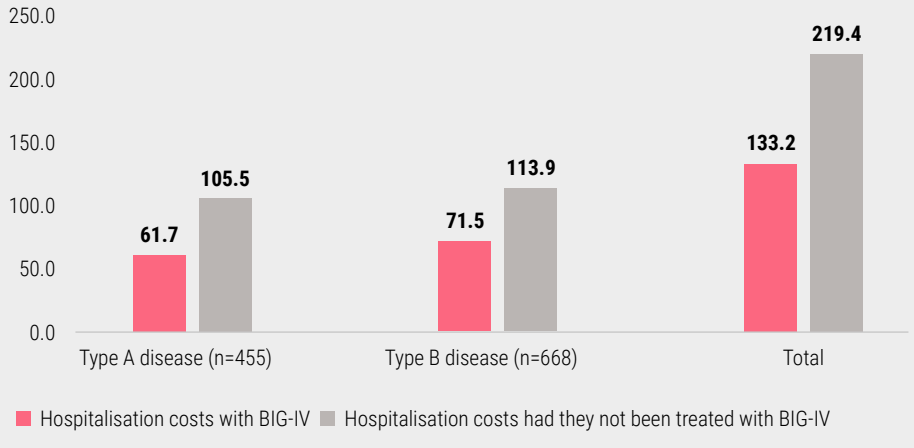
Source: *Carcedo Rodriguez (2021)*[39]

Infant botulism

Infant botulism is an acute and potentially lethal infectious disease in infants, resulting in flaccid paralysis[40]. Prior to the introduction of Botulism Intravenous Immune Globulin for Human Botulism (BIG-IV) in the United States in 2003, treatment for infant botulism patients was limited to nutritional care and respiratory support. Severely paralysed patients often required hospitalisation for several months before regaining sufficient strength to be discharged[40].

In the period from 2003 to 2015, BIG-IV was administered to 1,192 infant botulism patients in the United States, representing 100% of cases in the US. A study based on actual data from clinical practice evaluated the economic benefits of this drug, associated with reductions in hospitalisation, compared with data from the placebo group of the clinical trial conducted prior to its introduction. The cumulative length of hospital stay averted and cumulative hospital costs avoided using BIG-IV from 2003 to 2015 were estimated to be 66.9 years (average patient days: 2.2; placebo: 5.7) and $86.2 million (average hospital costs per patient: $118.6 million; placebo: $207.5), respectively (Figure 25)[40].

Figure 25. Hospitalisation costs for treatment of infant botulism in the United States, 2003-2015, in millions of dollars



Source: *Payne (2018)*[40]

➜ Indirect costs

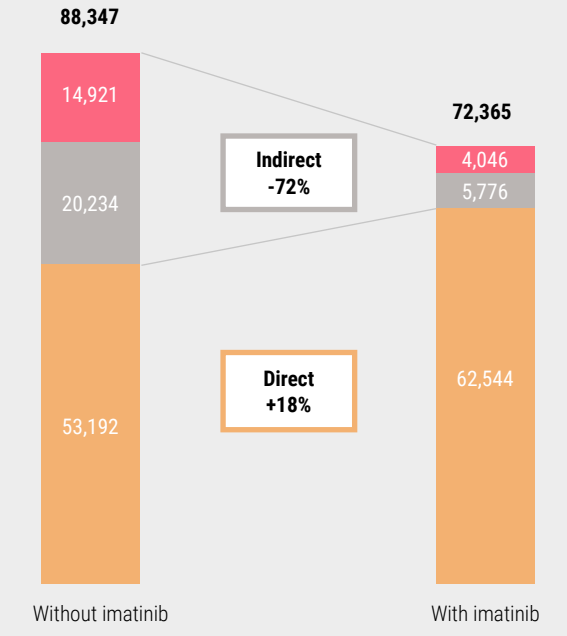
Orphan drugs not only generate savings for the healthcare system through improved patient health and reduced use of non-pharmacological resources but also enable those affected by a rare disease to return to their daily activities, including school or work. These indirect cost benefits are often not only limited to the person suffering from the rare disease, but also extend to the rest of their environment, especially in the case of children or when the patient requires substantial personal care. The following are concrete examples of the few studies that have evaluated how targeted treatments for rare diseases reduce the economic burden associated with indirect costs.

Chronic myeloid leukaemia

The introduction of imatinib, an oral tyrosine kinase inhibitor, has been reported to have radically changed the treatment of chronic myeloid leukaemia (CML), having a significant impact on extending patients' lives and improving their quality of life after diagnosis, making CML a chronic disease. The results of the pivotal seven-year clinical trial revealed an overall survival rate of 86% for patients treated with imatinib, with low relapse and progression rates, and an estimated progression-free overall survival of 93% at seven years[41].

A chinese economic model was designed based on real practice data, to project the clinical and long-term (5-year) cost-effectiveness of insurance coverage with and without imatinib as first-line treatment for patients with CML from a social perspective. This allowed the estimation of savings related to lost productivity of both caregivers and patients when the CLM patient was treated with this drug[41]. 72% reductions in costs associated with patient and caregiver work productivity were observed with the use of imatinib over 5 years. Thus, over this period, the total cumulative indirect costs amounted to $35,155 per patient not treated with imatinib (of which $20,234 related to work productivity losses for patients and $14,921 related to work productivity losses for caregivers), compared to $9,821 ($5,776; $4,046) per patient treated with the drug[41]. This reduction in indirect costs offset the increase in direct costs (mainly acquisition costs), resulting in a net saving in total costs to society. Overall, the total cost (direct and indirect) per patient at 5 years was $88,347 for untreated patients, compared to $72,365 per treated patient (Figure 26). This is an example of the importance of considering the social perspective when assessing the total impact of orphan drugs.

Figure 26. Total cumulative costs per patient for chronic myeloid leukaemia treatment in China, 5 years, in US$



Source: *Sheng (2017)*[41]

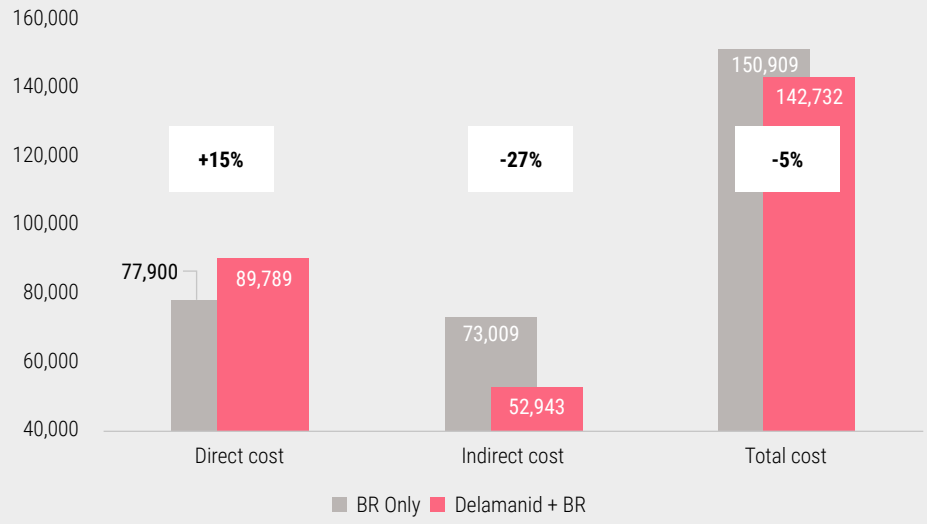
Multi-drug-resistant tuberculosis (MRD-TB)

In the MDR-TB setting, results from pivotal delamanid trials indicate that co-administration with an optimised background regimen (BR) of anti-TB drugs significantly improves sputum culture conversion rates at two months compared to BR plus placebo[42].

An economic model developed in Germany explored the costs and benefits associated with the addition of delamanid to BR and contrasted them with the exclusive use of BR. The analysis incorporated both direct and indirect costs. Over a 10-year time horizon, total costs per MDR-TB patient treated with delamanid for 6 months plus BR amounted to 142,732 euros, generating 8.47 QALYs. In contrast, total costs and QALYs for BR alone were 150,909 euros and 6.13, respectively. Therefore, the addition of delamanid to BR generated 5% of total saving per patient treated[42].

The decrease in total costs was exclusively attributed to a 27% reduction in indirect costs. Thus, while direct costs increased by 15% from 77,900 euros with BR alone to 88,789 euros with delamanid+ BR, indirect costs decreased from 73,009 euros to 52,943 euros, respectively (Figure 27)[42].

Figure 27. Costs per patient associated with treatment of multi-drug-resistant tuberculosis in Germany, 10 years, in euros



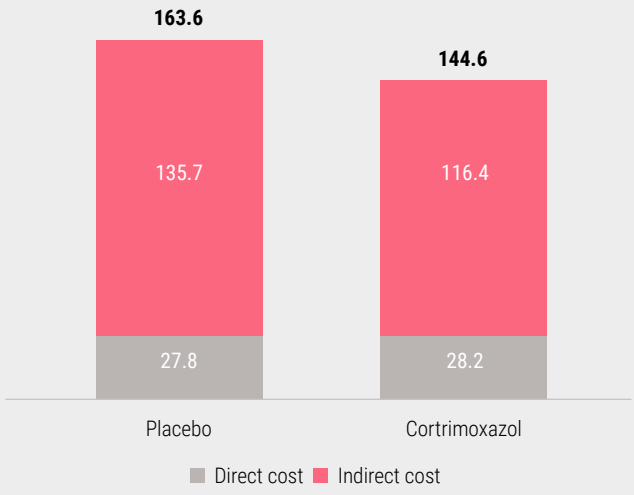
Note: ***BR:*** *optimised background treatment.*

Source: *Diel (2015)*[42]

Idiopathic interstitial pneumonia

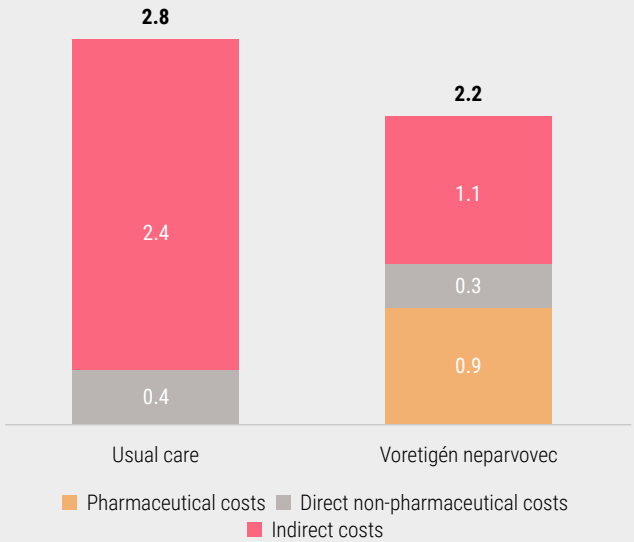
In a study of 20 patients with idiopathic interstitial pneumonia (IIP), the antibiotic cotrimoxazole showed significant improvements in clinical outcomes such as lung capacity[43]. Subsequently, a study of 80 patients evaluated the efficacy, safety and costs of adding co-trimoxazole to standard treatment for idiopathic pulmonary fibrosis (IPF), the most prevalent form of IIP in the UK[43]. According to the results, the annual indirect costs associated with treating all patients with this condition in the UK were reduced by 14%. These costs were £135.7 million with placebo, compared to £116.4 million with co-trimoxazole. This reduction allowed total costs to be reduced, generating savings, as indirect costs accounted for 80% of all costs to treat the disease (Figure 28)[43].

Figure 28. Costs of adding co-trimoxazole to the treatment of all patients with idiopathic pulmonary fibrosis in the UK, 12 months (2011), £million



Source: *Wilson (2014)*[43]

Figure 29. Lifetime costs associated with the treatment of 70 patients with retinal dystrophy associated with the biallelic RPE65 mutation, United States, millions of dollars



Source: *Johnson (2019)*[44]

Retinal dystrophy associated with biallelic RPE65 mutation

Another example is in the field of retinal dystrophy associated with the biallelic RPE65 mutation, an ultra-rare and severely progressive retinal disease. Voretigen neparvovec was the first gene therapy for patients with this disease. An economic model in the US has estimated the costs and benefits associated with the implementation of this therapy in 70 patients affected by this disease, from a social perspective, considering a time horizon of the patient's life. Voretigen neparvovec has been shown to generate more QALYs (18.1 vs. 8.6) and lower total costs ($2.2 million vs. 2.8 million) than the standard of care[44].

Savings were specifically observed in both the direct non-pharmacological costs associated with the use of this medicine ($0.3 million versus 0.4 million) and indirect costs ($1.1 million versus $2.4 million), offsetting the pharmaceutical cost of the medicine (about $0.9 million) (Figure 29)[44].

Hereditary angioedema

Finally, hereditary angioedema (HAE) manifests itself through acute attacks characterised by sudden swelling, pain and a significant reduction in quality of life. Several innovative drugs have been developed for the treatment of these acute attacks and the prevention of recurrence (human C1 esterase inhibitors and monoclonal anti-bodies), which have dramatically reduced the burden associated with this disease. By improving health and reducing disability, it allowed returning to work and schooling, and improving quality of life and survival[45,46].

Loss of educational and work opportunities is common with this disease. For example, a study on the socio-economic burden of HAE conducted in several EU countries, including Spain, found that patients experience a significant impact on their productivity, losing an average of 20 days of work or study per year due to the effects of the disease, with higher absenteeism if attacks were frequent or caused a high degree of pain[47]. Fifty-seven percent of patients with attacks at least once a month reported that HAE had interfered with their career or education, compared to 41% of patients with attacks less than once a month.

The availability of treatments and, in addition, the ability of patients to self-administer their therapies has been shown to have positive impacts on work productivity. In particular, self-administration of C1 esterase inhibitor therapy has shown marked improvements in several key areas compared to hospital or emergency department therapy, including a 65.5% reduction in lost work or school days (Figure 30).

Figure 30. Aspects of improvement with therapy administered in hospital or in the emergency department compared to self-administration of the C1 esterase inhibitor

Significant reduction in hospitalisations:

- The average annual number of hospitalisations has decreased from 16.8 to 2.1.

Efficiency in treatment delivery:

- Time to treatment has been reduced from 3.2 to 1.9 hours.
- Time to symptom improvement has decreased from 84 minutes to 54 minutes.
- Time to complete resolution of symptoms has been reduced from 12.8 to 10.8 hours.

Impact on productivity:

- Number of days lost from work or school has decreased from 23.3 to 7.1.

Source: *Petraroli (2015)*[48]

Bibliographic references

1. Farmaindustria. Proposals for Improving Patient Access to Orphan Medicines. 2023.
2. Zozaya, N, Villoro, R, Hidalgo, A, Sanz A, RADEEV Expert Group. Guía Metodológica de Evaluación Económica aplicada a Medicamentos Huérfanos. Max Weber Institute. Madrid; 2015.
3. Yang G, Cintina I, Pariser A, Oehrlein E, Sullivan J, Kennedy A. The national economic burden of rare disease in the United States in 2019. Orphanet J Rare Dis. 2022;17(1):163, doi: 10.1186/s13023-022-02299-5.
4. Lichtenberg F. The effect of new drugs on mortality from rare diseases and HIV. National Bureau of Economic Research; 2001.
5. Lichtenberg FR. The impact of new (orphan) drug approvals on premature mortality from rare diseases in the United States and France, 1999-2007. Eur J Health Econ HEPAC Dordr. 2013;14(1):41-56, doi: http://dx.doi.org/10.1007/s10198-011-0349-4.
6. Chambers JD, Thorat T, Wilkinson CL, Salem M, Subedi P, Kamal-Bahl SJ, et al. Estimating Population Health Benefits Associated with Specialty and Traditional Drugs in the Year Following Product Approval. Appl Health Econ Health Policy. 2017;15(2):227-35, doi: 10.1007/s40258-016-0291-9.
7. Wilsdon, Tim, Pistollato, Michele, Lawlor, Ryan. An evaluation of the economic and societal impact of the orphan medicine regulation. London: Charles River Associates; 2017.
8. Chambers JD, Silver MC, Berklein FC, Cohen JT, Neumann PJ. Orphan Drugs Offer Larger Health Gains but Less Favorable Cost-effectiveness than Non-orphan Drugs. J Gen Intern Med. 2020;35(9):2629, doi: 10.1007/s11606-020-05805-2.
9. Gatta G, Capocaccia R, Trama A, Mart'nez-Garc'a C. The Burden of Rare Cancers in Europe. In: Posada de la Paz M, Groft SC, editors. Rare Diseases Epidemiology. Dordrecht: Springer Netherlands; 2010. p. 285-303.
10. ESMO. Rare Cancers in Europe. [accessed 1 December 2023]. Available at: https://www.esmo.org/policy/rare-cancers-working-group/rare-cancers-in-europe.
11. Bhurke S. Updates from #ASCO23 and EHA on the efficacy and safety of, including molecular characterization and long-term follow-up in patients with mutant IDH1 AML and R/R MDS. 2023.
12. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Reagan PM, Miklos DB, et al. Comparison of 2-year outcomes with CAR T cells (ZUMA-1) vs salvage chemotherapy in refractory large B-cell lymphoma. Blood Adv. 2021;5(20):4149-55, doi: 10.1182/bloodadvances.2020003848.
13. Abramson JS, Solomon SR, Arnason J, Johnston PB, Glass B, Bachanova V, et al. Lisocabtagene maraleucel as second-line thera- py for large B-cell lymphoma: primary analysis of the phase 3 TRANSFORM study. Blood. 2023;141(14):1675-84, doi: 10.1182/blood.2022018730.
14. Laetsch TW, Maude SL, Rives S, Hiramatsu H, Bittencourt H, Bader P, et al. Three-Year Update of Tisagenlecleucel in Pediatric and Young Adult Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia in the ELIANA Trial. J Clin Oncol. 2023;41(9):1664-9, doi: 10.1200/JCO.22.00642.
15. Salles G, Schuster SJ, Dreyling M, Fischer L, Kuruvilla J, Patten PEM, et al. Efficacy comparison of tisagenlecleucel vs usual care in patients with relapsed or refractory follicular lymphoma. Blood Adv. 2022;6(22):5835-43, doi: 10.1182/bloodadvances.2022008150.
16. EMA. Kimmtrak. Epar. Medicine overview. 2022.
17. Nathan P, Hassel JC, Rutkowski P, Baurain J-F, Butler MO, Schlaak M, et al. Overall Survival Benefit with Tebentafusp in Metastatic Uveal Melanoma. N Engl J Med. 2021;385(13):1196-206, doi: 10.1056/NEJMoa2103485.
18. European Medicines Agency (EMA). Fact sheet Defitelio. 2018.
19. Burton BK, Balwani M, Feillet F, Barić I, Burrow TA, Camarena Grande C, et al. A Phase 3 Trial of Sebelipase Alfa in Lysosomal Acid Lipase Deficiency. N Engl J Med. 2015;373(11):1010-20, doi: 10.1056/NEJMoa1501365.
20. Schulz A, Ajayi T, Specchio N, de Los Reyes E, Gissen P, Ballon D, et al. Study of Intraventricular Cerliponase Alfa for CLN2 Disease. N Engl J Med. 2018;378(20):1898-907, doi: 10.1056/NEJMoa1712649.
21. Thomas J, Levy H, Amato S, Vockley J, Zori R, Dimmock D, et al. Pegvaliase for the treatment of phenylketonuria: Results of a long-term phase 3 clinical trial program (PRISM). Mol Genet Metab. 2018;124(1):27-38, doi: 10.1016/j.ymgme.2018.03.006.

22. Wensink D, Wagenmakers MAEM, Barman-Aksšzen J, Friesema ECH, Wilson JHP, van Rosmalen J, et al. Association of Afamelanotide With Improved Outcomes in Patients With Erythropoietic Protoporphyria in Clinical Practice. JAMA Dermatol. 2020;156(5):570-5, doi: 10.1001/jamadermatol.2020.0352.

23. Kanters TA, Hoogenboom-Plug I, Rutten-Van Mšlken MP, Redekop WK, van der Ploeg AT, Hakkaart L. Cost-effectiveness of enzyme replacement therapy with alglucosidase alfa in classic-infantile patients with Pompe disease. Orphanet J Rare Dis. 2014;9:75, doi: 10.1186/1750-1172-9-75.

24. Carretero Colomer M. Paroxysmal nocturnal haemoglobinuria. Approach to a rare disease. Offarm. March 1, 2009;28(3):60-1.

25. Coyle D, Cheung MC, Evans GA. Opportunity Cost of Funding Drugs for Rare Diseases: The Cost-Effectiveness of Eculizumab in Paroxysmal Nocturnal Haemoglobinuria. Med Decis Making. 2014;34(8):1016-29, doi: 10.1177/0272989X14539731.

26. Rubin JL, Lopez A, Booth J, Gunther P, Jena AB. Limitations of standard cost-effectiveness methods for health technology assessment of treatments for rare, chronic diseases: a case study of treatment for cystic fibrosis. J Med Econ. 2022;25(1):783-91, doi: 10.1080/13696998.2022.2077550.

27. Russell S, Bennett J, Wellman JA, Chung DC, Yu Z-F, Tillman A, et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. The Lancet. 2017;390(10097):849-60, doi: 10.1016/S0140-6736(17)31868-8.

28. European Medicines Agency (EMA). Fact sheet Spinraza. 2017.

29. Al-Zaidy SA, Mendell JR. From Clinical Trials to Clinical Practice: Practical Considerations for Gene Replacement Therapy in SMA Type 1. Pediatr Neurol. 2019;100:3-11, doi: 10.1016/j.pediatrneurol.2019.06.007.

30. Kohn DB, Booth C, Shaw KL, Xu-Bayford J, Garabedian E, Trevisan V, et al. Autologous Ex Vivo Lentiviral Gene Therapy for Adenosine Deaminase Deficiency. N Engl J Med. 2021;384(21):2002, doi: 10.1056/NEJMoa2027675.

31. Fumagalli F, Calbi V, Sora MGN, Sessa M, Baldoli C, Rancoita PMV, et al. Lentiviral haematopoietic stem-cell gene therapy for early-onset metachromatic leukodystrophy: long-term results from a non-randomised, open-label, phase 1/2 trial and expanded access. The Lancet. 2022;399(10322):372-83, doi: 10.1016/S0140-6736(21)02017-1.

32. Mehta S, Sastry BKS, Souza R, Torbicki A, Ghofrani H-A, Channick RN, et al. Macitentan Improves Health-Related Quality of Life for Patients With Pulmonary Arterial Hypertension: Results From the Randomized Controlled SERAPHIN Trial. Chest. 2017;151(1):106-18, doi: 10.1016/j.chest.2016.08.1473.

33. Andreu P, Karam J, Child C, Chiesi G, Cioffi G. The Burden of Rare Diseases: An Economic Evaluation. 2022.

34. Andreu P, Atay NJ, Piccinini E, Chiesi G, Cioffi G. Rare disease burden of care and the economic impact on citizens in Germany, France and Italy. 2023.

35. Tice J, Walton S, Herce-Hagiwara B, Fahim S, Moradi A, Sarker J, et al. Gene Therapy for Hemophilia B and An Update on Gene Therapy for Hemophilia A: Effectiveness and Value; Draft Evidence Report. Institute for Clinical and Economic Review. 2022.

36. Miners AH, Sabin CA, Tolley KH, Lee CA. Cost-Utility Analysis of Primary Prophylaxis versus Treatment On-Demand for Individuals with Severe Haemophilia. PharmacoEconomics. 2002;20(11):759-74, doi: 10.2165/00019053-200220110-00005.

37. Walter E, Bass J, Franklin TN. The effect of elexacaftor/tezacaftor/ ivacaftor on hospital days and costs: A single-center experience. Pediatr Pulmonol. 2020:352-3.

38. Mamolo C, Welch V, Walter RB, Cappelleri JC, Brockbank J, Cawson M, et al. Budget Impact Analysis of Gemtuzumab Ozogamicin for the Treatment of CD33-Positive Acute Myeloid Leukemia. Pharmacoeconomics. 2021;39(1):121-31, doi: 10.1007/s40273-020- 00976-6.

39. Carcedo Rodriguez D, Artola Urain T, Chinea Rodriguez A, Garc'a Torres E, González Vicent M, Gutiérrez Garc'a G, et al. Cost-effec- tiveness analysis of defibrotide in the treatment of patients with severe veno-occlusive disease/sinusoidal obstructive syn- drome with multiorgan dysfunction following hematopoietic cell transplantation in Spain. J Med Econ. 2021;24(1):628-36, doi: 10.1080/13696998.2021.1916749.

40. Payne JR, Khouri JM, Jewell NP, Arnon SS. Efficacy of Human Botulism Immune Globulin for the Treatment of Infant Botulism: The First 12 Years Post Licensure. J Pediatr. 2018;193:172-7, doi: 10.1016/j.jpeds.2017.10.035.

41. Sheng G, Chen S, Dong C, Zhang R, Miao M, Wu D, et al. Societal implications of medical insurance coverage for imatinib as first-line treatment of chronic myeloid leukemia in China: a cost-effectiveness analysis. J Med Econ. 2017;20(4):371-81, doi: 10.1080/13696998.2016.1271336.

42. Diel R, Hittel N, Schaberg T. Cost effectiveness of treating multi-drug resistant tuberculosis by adding DeltybaTM to background regimens in Germany. Respir Med. 2015;109(5):632-41, doi: 10.1016/j.rmed.2015.01.017.

43. Wilson ECF, Shulgina L, Cahn AP, Chilvers ER, Parfrey H, Clark AB, et al. Treating Idiopathic Pulmonary Fibrosis with the Addition of Co-Trimoxazole: An Economic Evaluation Alongside a Randomised Controlled Trial. PharmacoEconomics. 2014;32(1):87-99, doi: 10.1007/s40273-013-0112-z.

44. Johnson S, Buessing M, O'Connell T, Pitluck S, Ciulla TA. Cost-effectiveness of Voretigene Neparvovec-rzyl vs Standard Care for RPE65-Mediated Inherited Retinal Disease. JAMA Ophthalmol. 2019;137(10):1115-23, doi: 10.1001/jamaophthalmol.2019.2512.

45. Lumry WR. Hereditary Angioedema: The Economics of Treatment of an Orphan Disease. Front Med. 2018;5:22, doi: 10.3389/fmed.2018.00022.

46. Caballero T. Treatment of Hereditary Angioedema. J Investig Allergol Clin Immunol. 2021;31(1):1-16, doi: 10.18176/jiaci.0653.

47. Aygören-Pürsün E, Bygum A, Beusterien K, Hautamaki E, Sisic Z, Wait S, et al. Socioeconomic burden of hereditary angioedema: results from the hereditary angioedema burden of illness study in Europe. Orphanet J Rare Dis. 2014;9:99, doi: 10.1186/1750-1172-9-99.

48 . Petraroli A, Squeglia V, Di Paola N, Barbarino A, Bova M, Span˜ R, et al. Home Therapy with Plasma-Derived C1 Inhibitor: A Strategy to Improve Clinical Outcomes and Costs in Hereditary Angioedema. Int Arch Allergy Immunol. 2015;166(4):259-66, doi: 10.1159/0003813411.

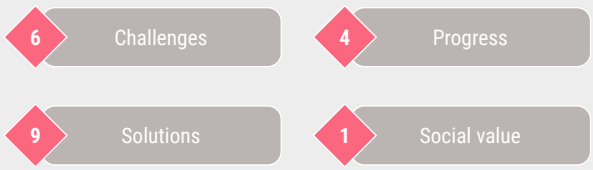
Chapter 5

The opinion of relevant actors of the system

5.1. Context and methodology

The aim of this questionnaire was to gather the opinion of different relevant actors in the health system on the issues addressed in this report. The survey was divided into four distinct sections, with a total of 20 questions. The first section included questions on the main challenges faced by the OMPs in the field of research, access and the timing of the authorisation, evaluation and funding process. The second section focused on progress in these areas, while the third and fourth sections grouped questions on possible solutions and on the societal value of OMPs (Figure 1).

Figure 1. Topics and number of questions in the questionnaire



Seventy stakeholders with different profiles were invited to participate in this online survey: managers, clinicians, health technology assessment agencies, patient associations and scientific societies, among others. A total of 30 stakeholders responded to the survey (43% response rate), with the most representative group being other profiles (health economists, researchers and health law experts) (30%) (Table 1).

Table 1. Distribution of participants in the survey, according to profile

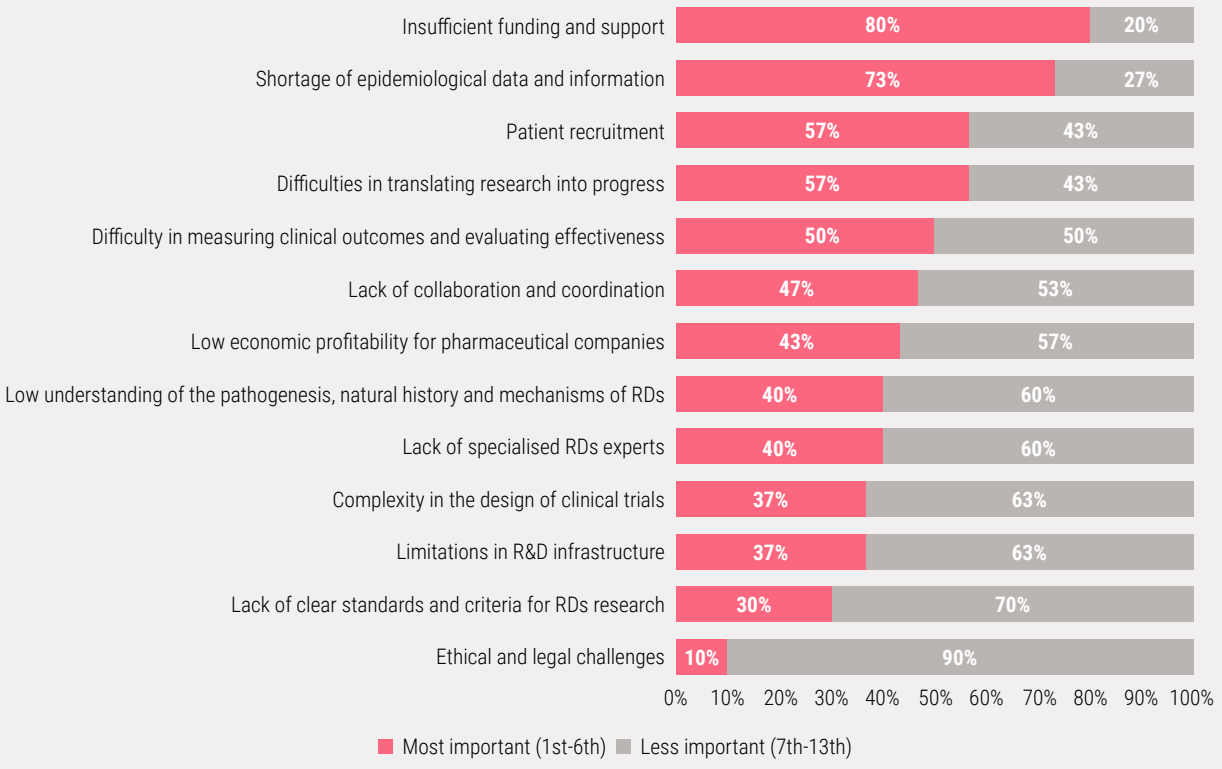
	Participants	% Participants	Answers	% Answers
Health authorities	27	39%	8	27%
Scientific societies	14	20%	6	20%
HTA Agencies	8	11%	1	3%
Patient associations	7	10%	6	20%
Others (health economists, researchers, lawyers...)	14	20%	9	30%
TOTAL	70	100%	30	100%

5.2. Analysis of the questionnaire

➜ Section I. Challenges

First, respondents were asked to rank 13 challenges in the field of RDs research and OMPs development in order of importance. To facilitate the interpretation of the data, the answers have been divided into "most important" if they were ranked in positions 1-6 and "least important" for positions 7-13. Insufficient funding and support were considered the most important challenge for 80% of the consulted stakeholders. Other challenges voted as important included the scarcity of information and epidemiological data as well as patient recruitment. In contrast, ethical and legal challenges and the lack of clear research standards and criteria were the least important criteria (Figure 2).

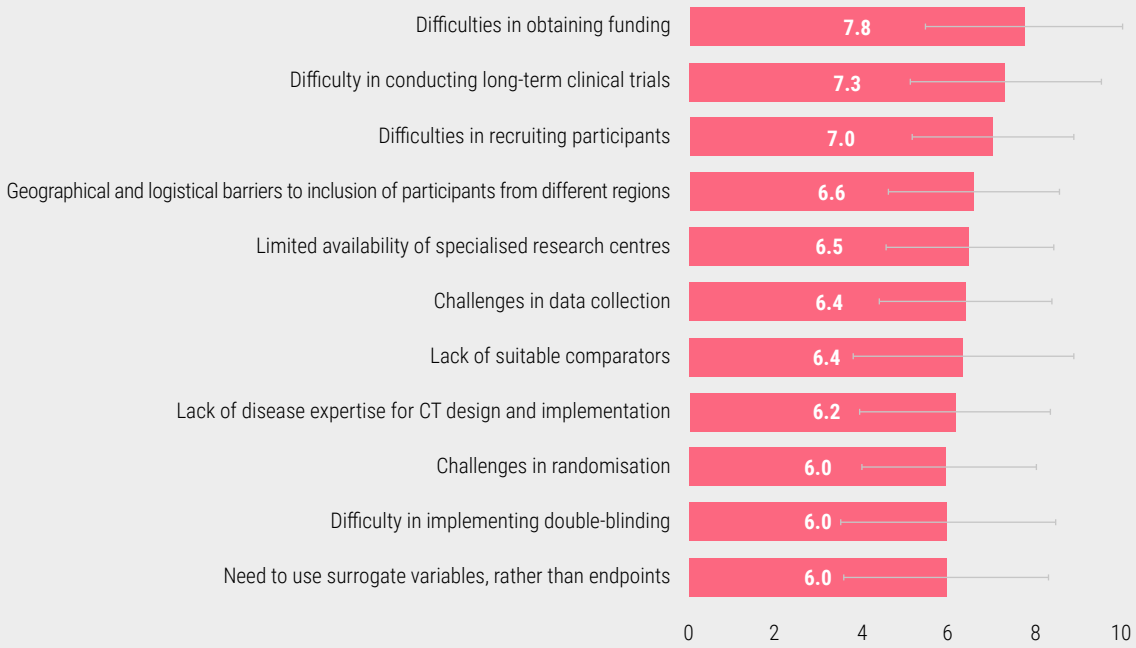
Figure 2. Q1. Rank the following general challenges in the field of rare disease research and orphan drug development by importance, from most (1st) to least important (13th) (N=30)



Note: ***RDs:*** *rare diseases.*

Respondents were then asked to rate from 0 to 10 the importance of 11 challenges regarding conducting clinical trials (CT) in OMPs. The stakeholders identified difficulties in obtaining funding and the difficulty in conducting long-term CTs as the two biggest challenges, with an average score of 7.8 and 7.3 out of 10, respectively. On the contrary, the need to use surrogate variables, the difficulty in implementing double-blinding and the challenges in randomisation were the challenges rated as least important by the agents, with 6.0 points on average. Based on the standard deviation (SD) of the responses, difficulties in recruiting participants and the limited availability of specialised research centres are the measures on which there is the greatest consensus (SD of 1.9 for both). On the other hand, there is a greater disparity of opinion on the lack of suitable comparators (SD: 2.6) and the difficulty in implementing double-blinding (SD: 2.5) (Figure 3).

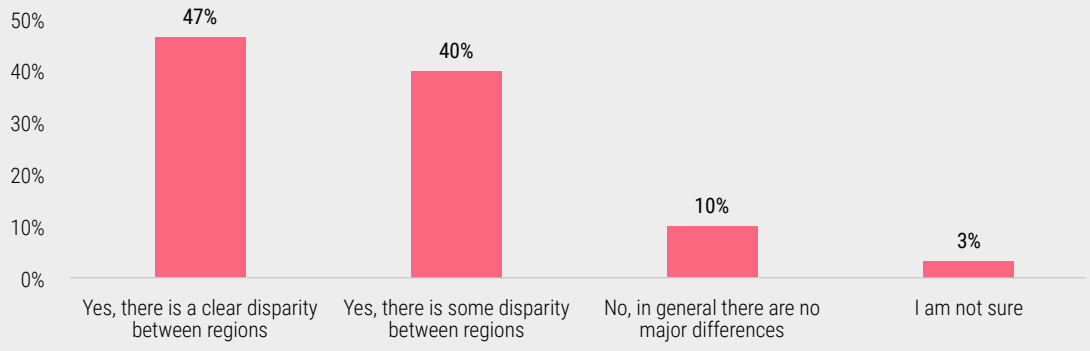
Figure 3. Q2. Please rate from 0 to 10 the following specific challenges for conducting clinical trials of orphan drugs, where 0 represents no importance and 10 represents very important (average score and standard deviation). (N=30)



Note: ***CT:*** *clinical trials.*

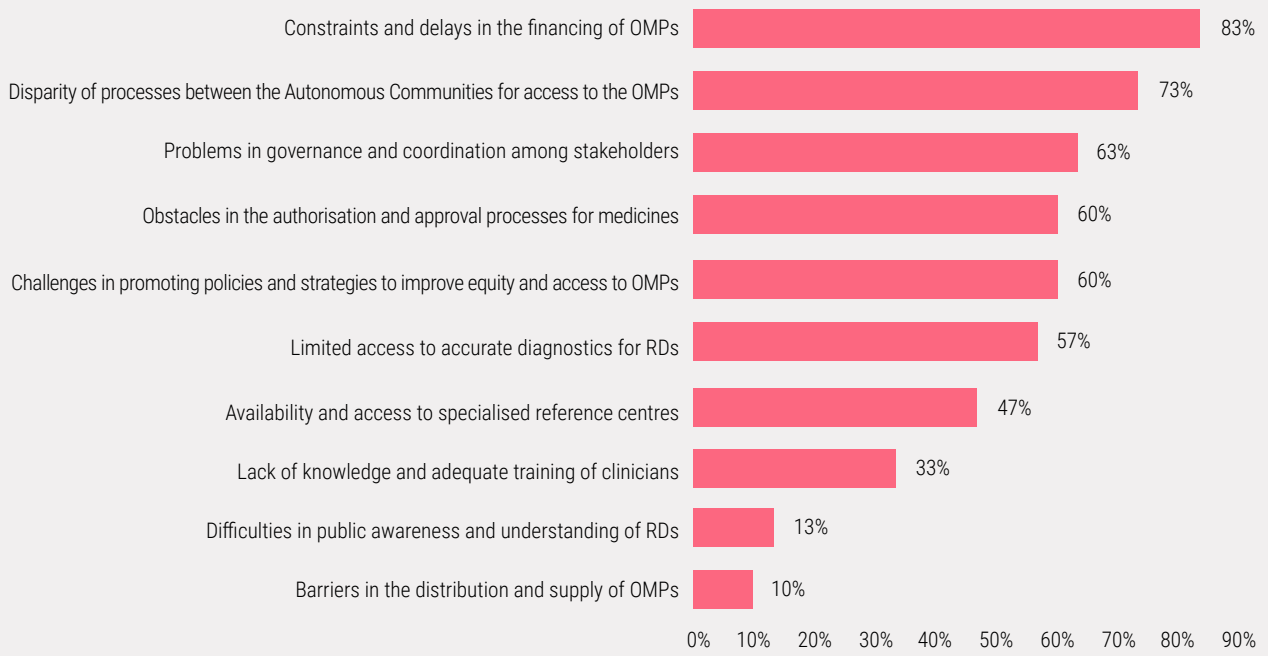
As to whether there are differences in access and equity to OMPs between regions, 87% of respondents believe that there are differences. Almost half of the respondents (47%) think that there are clear disparities between regions. On the contrary, 10% of the actors thought that there are generally no major differences (Figure 4).

Figure 4. Q3. Do you consider that there are differences in access and equity of access to OMPs between regions in Spain? (N=30)



Regarding the challenges on equity and access to OMPs in Spain, experts were asked to select the top 5 challenges in this area. Limitations and delays in financing and the disparity of processes between the Autonomous Communities were the top 2 challenges, selected by 83% and 73% of respondents, respectively. On the other hand, barriers in the distribution and supply of OMPs as well as public awareness and understanding of RDs are the least important challenges for respondents (Figure 5).

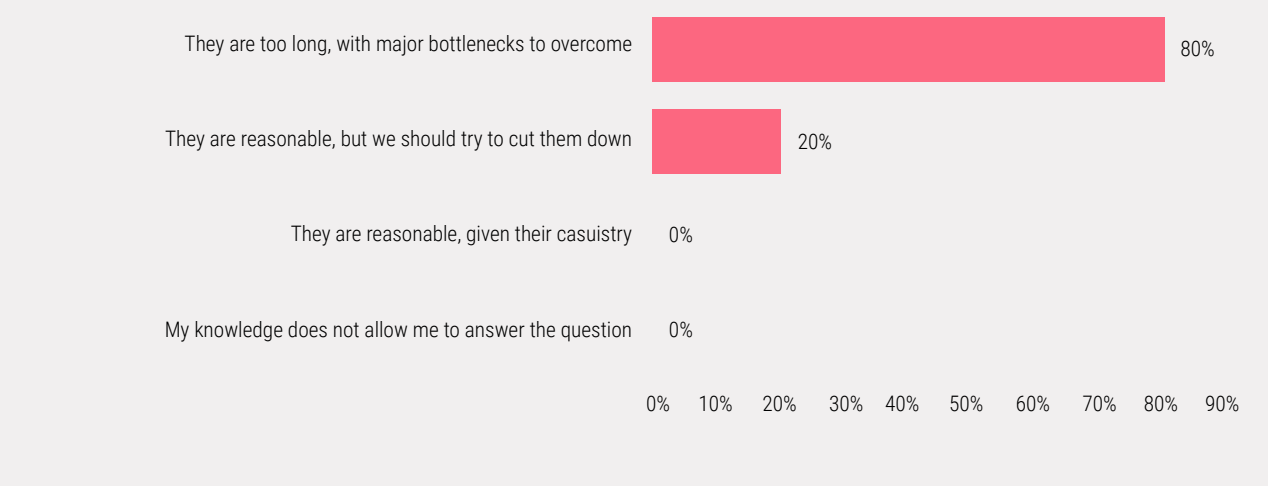
Figure 5. Q4. What five challenges you consider most important in terms of equity and access to orphan drugs in Spain? (select 5) (N=30)



Note: ***ACs:*** *Autonomous Communities;* ***RDs:*** *rare diseases;* ***OMPs:*** *orphan drugs.*

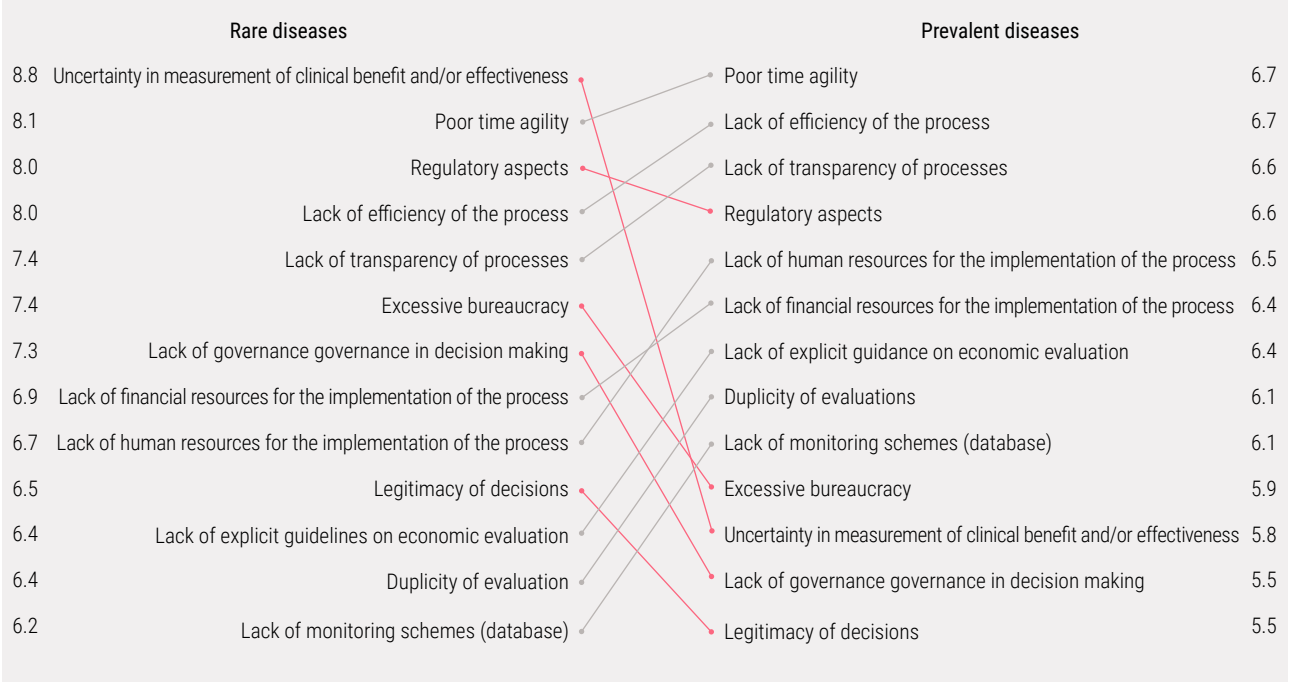
A large majority of respondents (80%) believe that the current timelines for the authorisation, evaluation and pricing of orphan drugs in Spain are too long, with bottlenecks that need to be addressed. Likewise, 20% say that there are reasonable, but that efforts should be made to cut them even further. It is noteworthy that none of the respondents indicated that the current timelines seem reasonable to them (Figure 6).

Figure 6. Q5. What is your opinion on the current timing of the overall process of authorisation, evaluation and pricing of orphan drugs in Spain? (N=30)



Next, stakeholders were asked to rate the importance of 13 items regarding the authorisation, evaluation and funding process for OMPs by the NHS, in comparison to medicines treating prevalent diseases. The greatest uncertainty in the measurement of clinical benefit and/or effectiveness (8.8 on average out of 10), followed by poor timeline management (8.1) and regulatory aspects and lack of efficiency of the process (both 8.0 on average) were the 3 major aspects. On the contrary, the lack of monitoring schemes (6.2), the duplication of evaluations and the lack of explicit guidelines on economic evaluation are the least important aspects for experts (both 6.4 on average). The main difference with respect to prevalent diseases lies in the uncertainty in the measurement of clinical benefit, which goes from being the most important aspect in OMPs to being the tenth most important for prevalent diseases. Also, excessive bureaucracy, lack of governance and legitimacy of decisions are more important in OMPs than in medicines for prevalent diseases (Figure 7).

Figure 7. Q6. Please rate from 0 to 10 the importance of the following aspects in the process of authorisation, evaluation and financing of orphan medicinal products in the NHS, compared to medicinal products intended to treat prevalent diseases, where 0 represents no importance and 10 represents very important (average score)
(N=30)



➜ Section II. Progress

In terms of research alternatives and techniques that have been introduced to improve the design and conduct of clinical trials in RDs, 73% of respondents selected international collaboration and research networks as the most important element, followed by the use of historical data and controls. In contrast, respondents gave less importance to studies with n=1 (Table 2).

The key issues discussed by the experts in the dedicated open space were the use of long-term extension studies to reaffirm/disprove evidence, the use of add-on designs to minimise placebo rejection, the use of enriched populations, and the use of sequential designs to end the trial as soon as definitive results are obtained.

Table 2. Q7. Rank, according to importance (from most to least important), the research alternatives and techniques that have been introduced to improve the design and execution of clinical trials in rare diseases average score (N=30)

	1º	2º	3º	4º	5º	Average
International collaboration and research networks	73%	7%	10%	0%	10%	1,7
Use of historical data and historical controls	13%	27%	20%	23%	17%	3,0
Adaptive clinical trials	7%	50%	27%	10%	7%	2,6
Basket clinical trials	3%	13%	27%	47%	10%	3,5
Tests with n=1	3%	3%	17%	20%	57%	4,2

According to the respondents, the most impactful development in terms of access and equity of OMPs were the EMA special authorisation programmes, followed by the regulation on availability of medicines in special situations and early access or compassionate use. In contrast, the development of a national RD strategy was the least impactful development for 43% of the experts, although it was selected as the most impactful measure by 10% of the experts (Table 3).

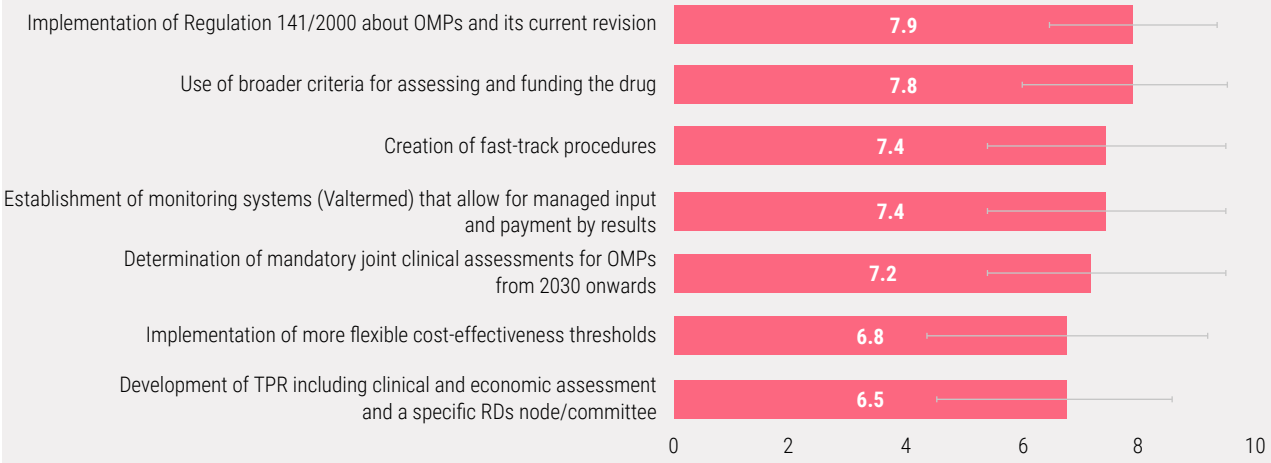
Table 3. Q8. In your opinion, what are the developments that have had the greatest impact in terms of access and equity to orphan drugs? (rank in order of greatest to least impact, with 1st having the greatest impact and 6th having the least impact) (N=30)

	1º	2º	3º	4º	5º	6º	Average
Special EMA authorisation programmes (conditional, accelerated, exceptional approval)	47%	20%	17%	7%	3%	7%	2,2
The regulation (RD 1015/2009) on the availability of medicines in special situations	20%	20%	27%	27%	0%	7%	2,9
Early access or compassionate use programmes	17%	27%	13%	20%	20%	3%	3,1
The development of a national rare disease strategy	10%	3%	10%	10%	23%	43%	4,6
The use of pay-for-performance agreements for these products	3%	23%	20%	27%	3%	23%	3,7
The extensive network of CSUR in Spain	3%	7%	13%	10%	50%	17%	4,5

Note: ***CSUR:*** *Reference Centres, Services and Units;* ***EMA:*** *European Medicines Agency*

The implementation of the Regulation 141/2000 and the use of broader criteria for drug evaluation and funding were identified by stakeholders as the most significant advances in the authorisation, evaluation and funding of OMPs, with an average score of 7.9 and 7.8 out of 10, respectively. The preparation of Therapeutic Positioning Reports (TPR) with the inclusion of clinical and economic evaluation with a specific node/committee for RDs is the least significant advance for the experts, with an average score of 6.5 out of 10. On the other hand, the implementation of Regulation 141/2000 is the progress on which there is the greatest consensus (SD: 1.4), while the greatest differences are found in the obligatory nature of the 'joint clinical assessments' in OMPs and the application of more flexible cost-effectiveness thresholds (SD: 2.4 for both) (Figure 8).

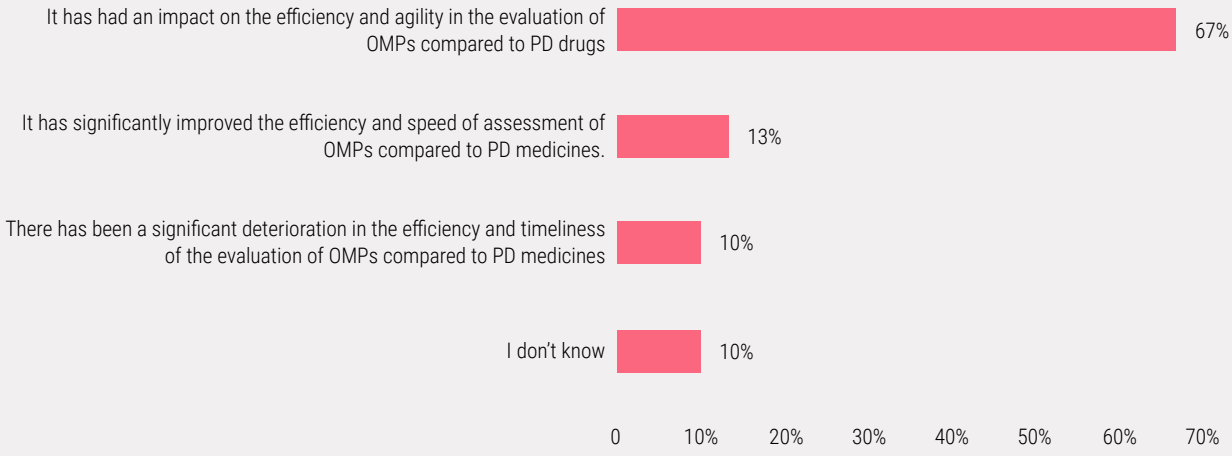
Figure 8. Q9. What are the most significant advances made in the authorisation, evaluation and financing of orphan drugs (score from 0 to 10, with 0 being the least significant and 10 being the most significant) (average score and standard deviation) (N=30)



Note: ***RDs:*** *Rare diseases;* ***TPR:*** *Therapeutic Positioning Reports;* ***OMPs:*** *Orphan medicinal products*

For the majority of respondents (67%), the revision of the procedure and approval of TPRs in Spain, with a specific assessment node for OMPs, has had some positive impact on the efficiency and speed of the assessment of OMPs for medicines for common diseases. While 13% of respondents felt that this impact was noticeable, 10% felt that this revision had a negative impact, significantly worsening the efficiency and speed of the evaluation of OMPs (Figure 9).

Figure 9. Q10. What impact do you think the revision of the procedure and approval of TPRs in Spain, which includes the creation of a specific node for the assessment of OMPs, has had on medicines prevalent diseases (N=30)?

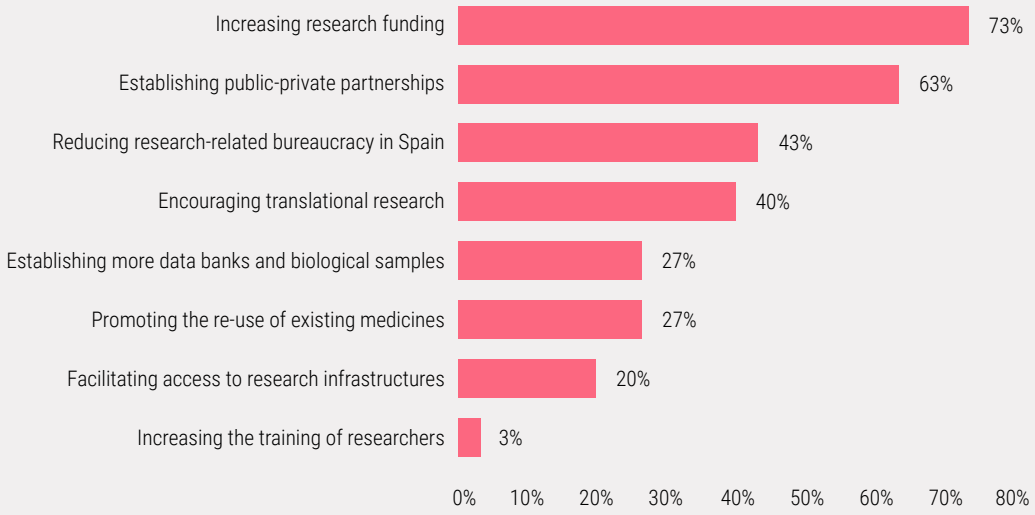


Note: ***OMPs:*** *orphan medicinal products;* ***PD:*** *prevalent diseases.*

➜ Section III. Solutions

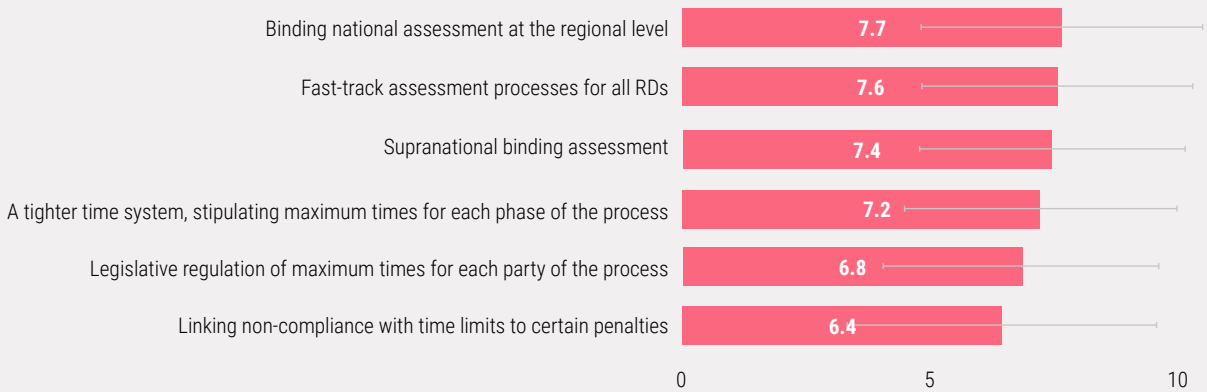
Increasing research funding and establishing public-private partnerships were the actions most supported by stakeholders (selected by 73% and 63% respectively) to address the challenges in the field of research and development. In contrast, increasing the training of researchers and facilitating access to research infrastructures were only supported by 3% and 20% of experts, respectively (Figure 10).

Figure 10. Q11. What measures do you consider most important to address the challenges in the field research and development of medicines to treat rare diseases? (select 3) (N=30)



In a hypothetical situation, with different possible measures to speed up OMPs evaluation and funding times in Spain, respondents were asked to rate the degree to which each measure would help, on a scale of 0 to 10. Respondents indicated that a binding national evaluation at the regional level would help the most (7.7 average out of 10) followed by a fast-track assessment process for all rare diseases (7.6 average). Sentencing non-compliance with timelines to certain penalties (6.4) and legislative regulation on maximum times for each part of the process (6.8) are the measures that would help the least according to respondents (Figure 11).

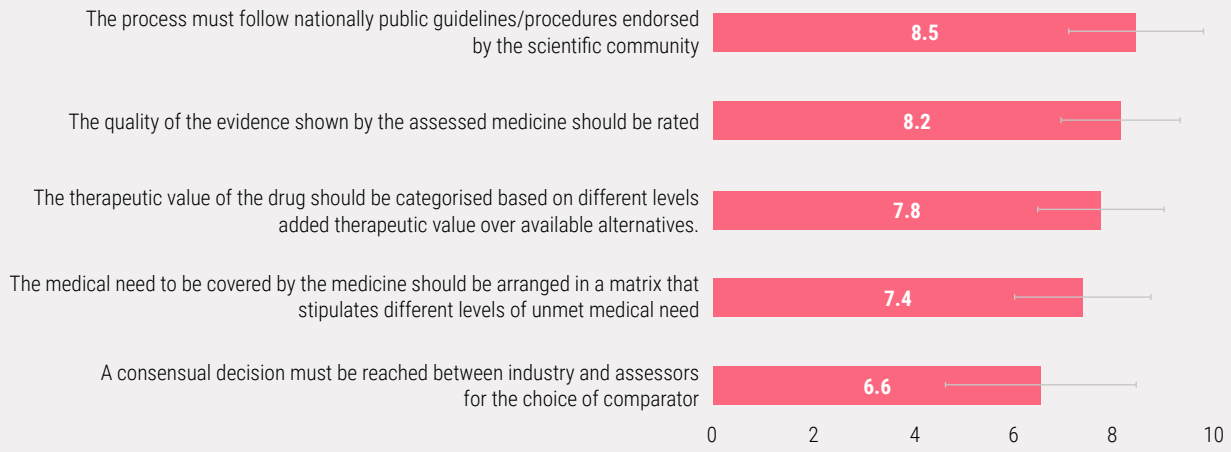
Figure 11. Q12. What measures do you think would help to speed up the time taken to evaluate and finance the OMPs in Spain (score from 0 to 10, where 0 would represent no help and 10 would represent considerable help) (average score and standard deviation) (N=30)



Note: ***RDs:*** *rare diseases.*

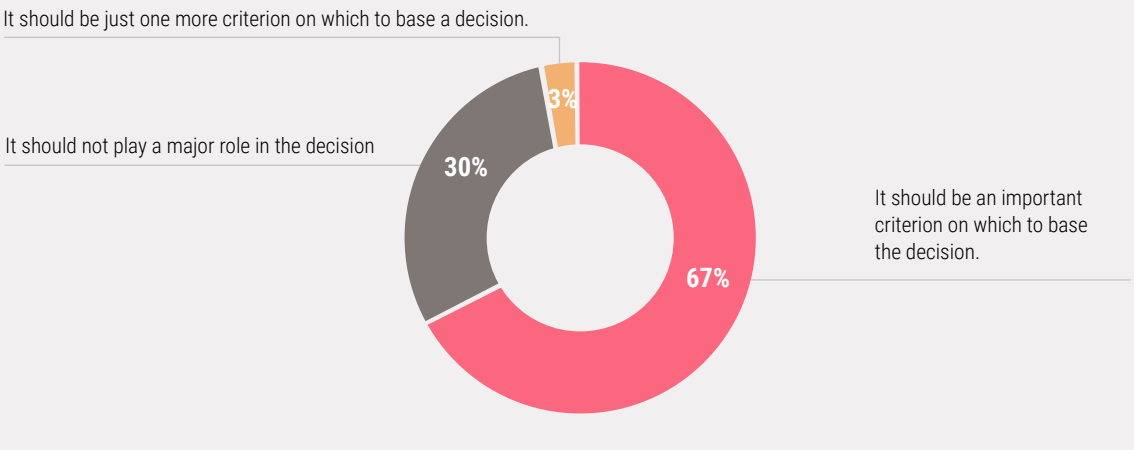
Regarding the inclusion of a clinical evaluation within the TPRs, the agents believe that the process should follow national public guidelines/procedures endorsed by the scientific community, and to a lesser extent, classify the quality of the evidence shown by the medicine and categorise the therapeutic value of the drug at different levels over the available alternatives. They also consider it less relevant to reach a consensual decision between the industry and the assessors for the choice of the comparator. However, this statement is the one with the greatest discrepancy among respondents, with a SD of 1.9. On the contrary, there is greater consensus that the quality of evidence shown by the medicine should be rated, with a deviation of 1.2 (Figure 12).

Figure 12. Q13. Please rate from 0 to 10 your level of agreement with the following items regarding the clinical evaluation of orphan drugs in Therapeutic Positioning Reports (TPRs), with 0 being strongly disagree and 10 being strongly agree (mean score and standard deviation). (N=30)



Regarding the role of the economic evaluation should play in informing pricing and financing decisions for a new OMP, the majority of experts (67%) thought that economic evaluation should be an important criterion on which to base the decision, while 30% indicate that it should be an additional, but not the only criterion. For 3%, economic evaluation should not play an important role in the decision (Figure 13).

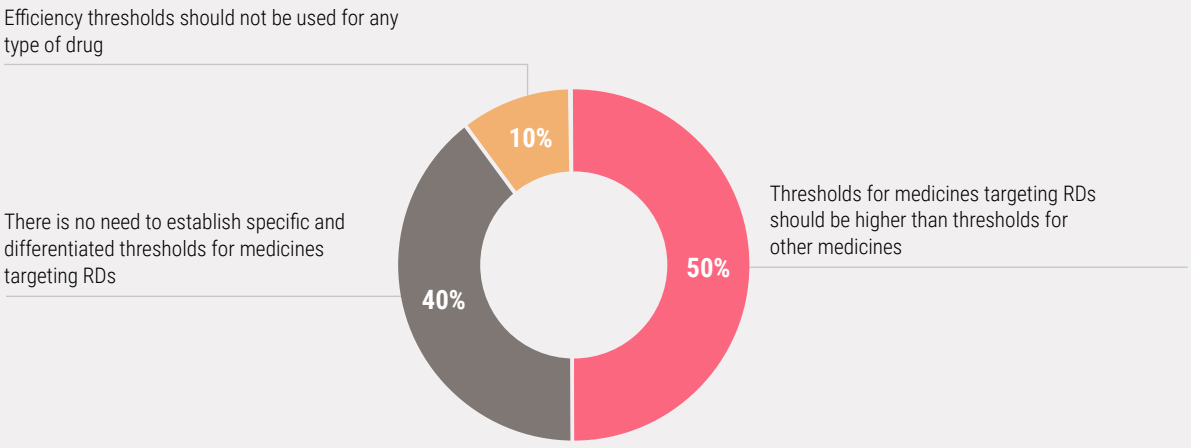
Figure 13. Q14. What is your opinion on the role of economic evaluation (efficiency or cost-effectiveness) in informing pricing and funding decisions for a new OMP (N=30)?



Regarding the use of a willingness-to-pay thresholds per Quality Adjusted Life Year (QALY) gained with the OMPs in relation to the use of the comparator, there is no consensus among the stakeholders. Half of the respondents thought that thresholds for medicines targeted at RDs should be higher than for other medicines, while 40% considered that there is no need for thresholds.

On the other hand, 10% do not support the use of willingness-to-pay thresholds for any medicine (Figure 14).

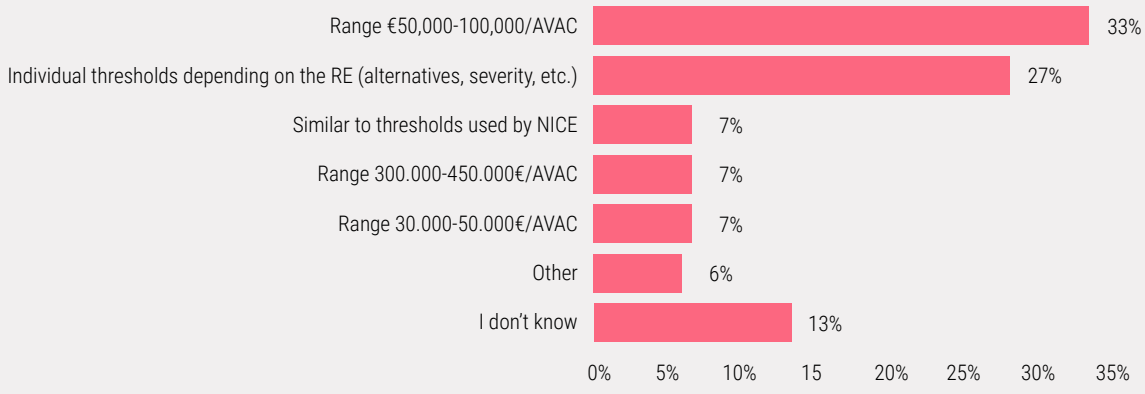
Figure 14. Q15. Do you think there should be differentiated thresholds of willingness to pay for quality-adjusted life years (QALYs) gained for rare disease targeted medicines? (N=30)



Note: ***RDs:*** *rare diseases*

Agents who responded that thresholds for RDs medicines should be higher than thresholds for other medicines were asked to elaborate on their response, including what values could be considered. One third of them indicated that thresholds between €50,000-100,000/AVAC should be considered for these medicines, while 14% of agents indicated thresholds similar to those used by the NICE (for rare, severely disabling diseases with a high unmet need, NICE uses thresholds of €116,500/AVAC- €350,000/AVAC). Also, for a quarter of respondents, individual thresholds should be set according to the rare disease in question (Figure 15).

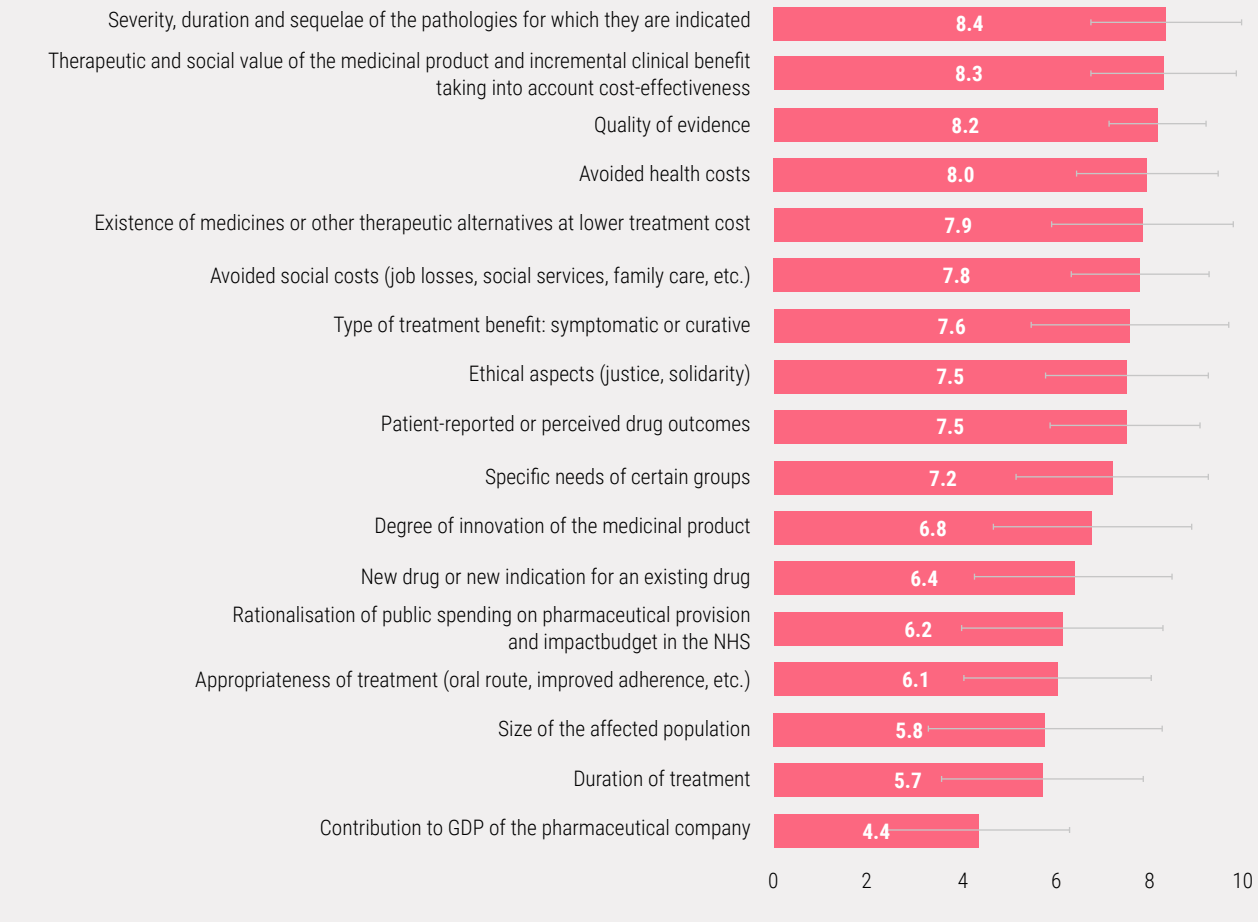
Figure 15. Q16. Given that you are of the opinion that thresholds for medicines targeting rare diseases should be higher than thresholds for other medicines, please detail your response, including what values could be considered (N=15)



Note: ***NICE:*** *National Institute for Health and Care Excellence.*

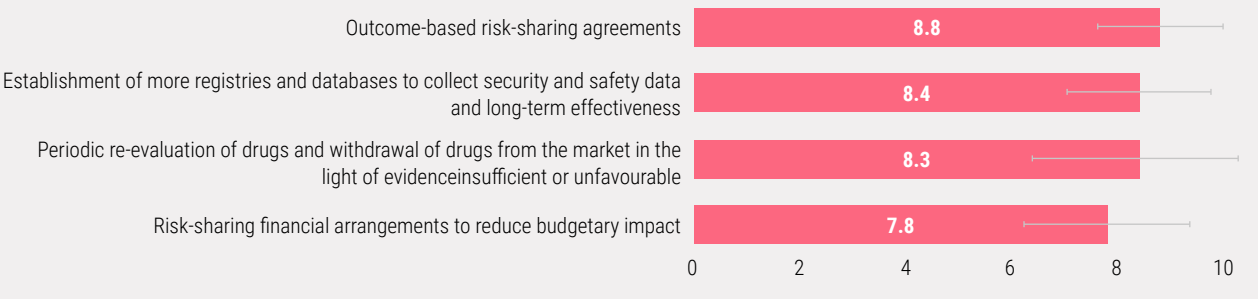
With regard to the weight that the different criteria should have for the pricing and reimbursement decision of OMPs in Spain, the agents valued the severity, duration and sequelae of the pathologies (weight of 8.4 out of 10) as the most important element, followed by the therapeutic and social value and the incremental clinical benefit brought by the medicine as well as the quality of the evidence (8.3 and 8.2, respectively). In contrast, the contribution to the pharmaceutical company's GDP, the duration of treatment and the size of the affected population do not seem relevant to respondents.

Figure 16. Q17. Please specify a weight for the criteria that you think should be considered in the pricing and reimbursement of medicines in general, scoring 0 if you think the criterion should not be taken into account and with 10 if you think it has a very important weight (average score and standard deviation) (N=30)



With regards to the possible measures which could reduce uncertainty in relation to the evidence generated by RDs, stakeholders considered the use of outcome-based risk-sharing agreements to be mostly important (8.8 out of 10), followed by the establishment of more registries and databases (8.4). The highest degree of consensus was on the measure of risk-sharing arrangements (SD: 1.2), while the greatest disparity of opinion was on periodic re-evaluation of drugs (SD: 1.9) (Figure 17).

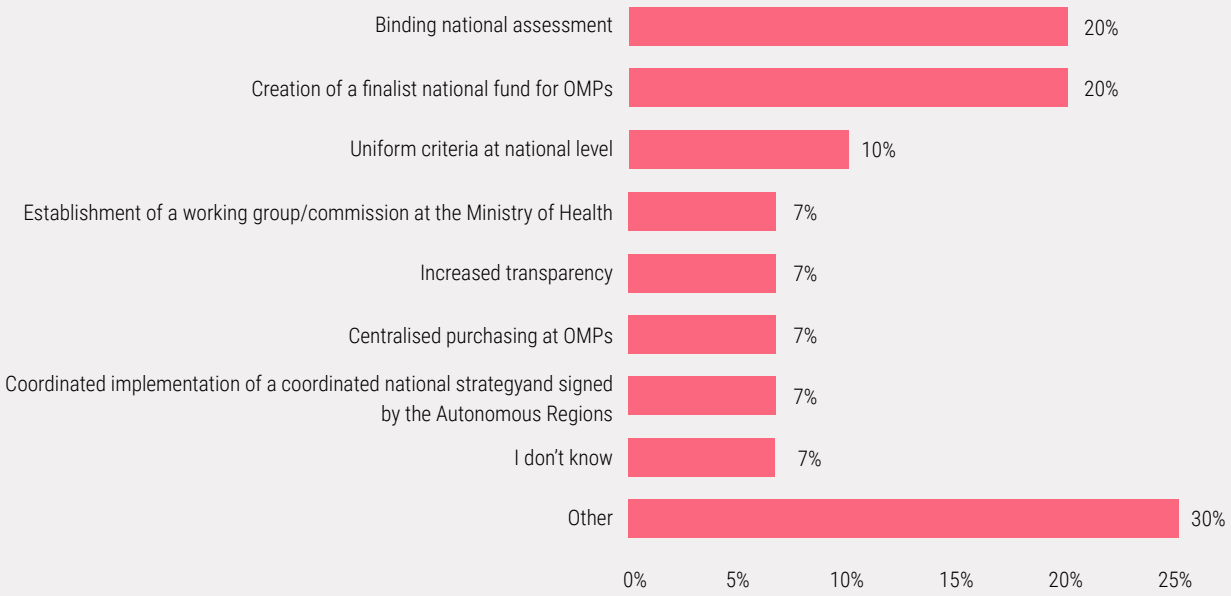
Figure 17. Q18. On a scale of 0 to 10, please rate the importance of the following measures to promote uncertainty reduction in relation to the evidence generated by the OMPs, where 0 represents no importance and 10 represents very important (average score and standard deviation). (N=30)



Note: ***BD:*** *databases*

Regarding possible concrete measures that could reduce disparities in access and equity in OMPs, 20% of the actors indicated that the main measures to be taken would be to establish an evaluation at the national level and for this to be binding in the different ACs as well as creating a national fund for this purpose. Among the "other contributions" suggested by the stakeholders were to carry out an annual evaluation and report on access in each Autonomous Region, to think access at the European level, to increase public-private collaboration or to use payment by results for medicines with high uncertainty (Figure 18).

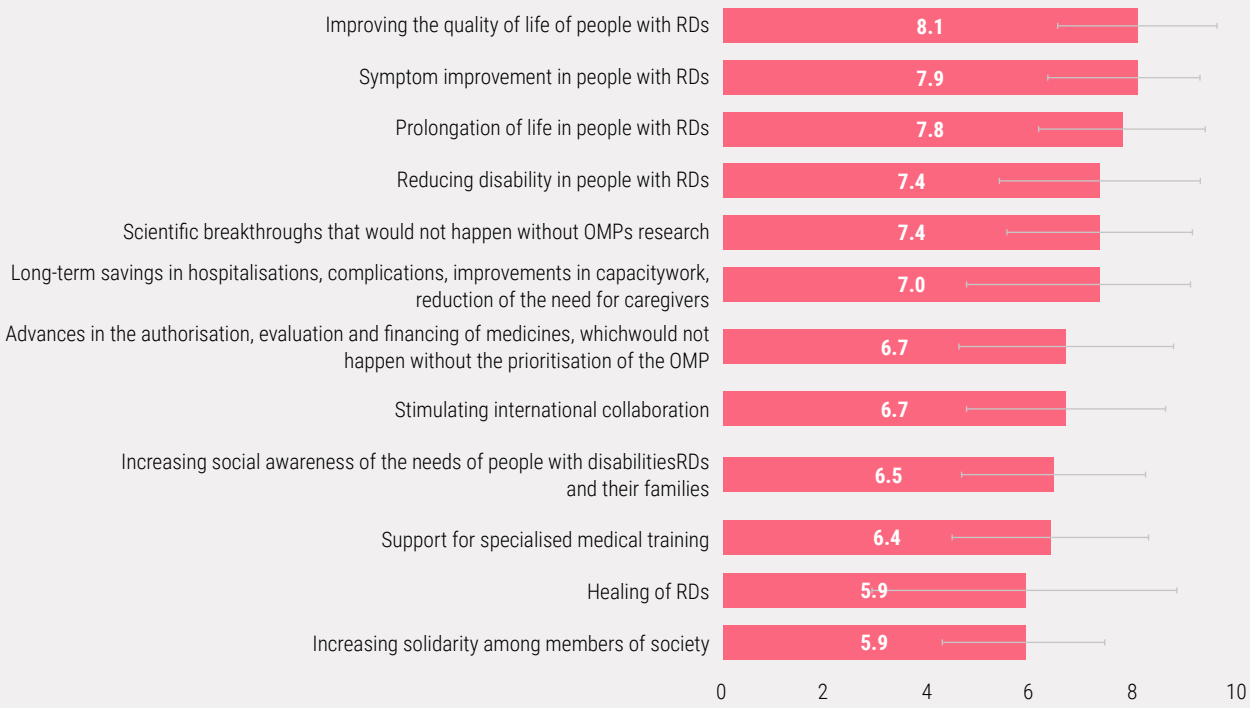
Figure 18. Q19. Excluding evaluation and funding issues, what concrete measures do you think could be implemented to reduce disparities in access and equity of orphan drugs in Spain?
(N=30)



➜ Section IV. Social value

Finally, the experts were asked to rate the most important value of orphan drugs, with 0 being the lowest contribution and 10 being the highest possible contribution. Improvement of quality of life, improvement of symptoms and prolongation of life were the 3 highest rated contributions, with an average score of 8.1, 7.9 and 7.8 respectively. The lowest rated contributions were increasing solidarity among members of society (5.9 out of 10), curing rare diseases (5.9) and supporting specialised medical training (6.4). Curing rare diseases was the contribution where there was the greatest lack of consensus. (SD:3.0) (Figure 19).

Figura 19. Q20. Please rate the main value contributions you think orphan drugs have made, where 0 indicates the lowest contribution and 10 the highest possible contribution (average score and standard deviation). (N=30)



Note: ***RDs:*** *rare diseases;* ***OMPs:*** *orphan medicinal products.*

Key messages

Challenges

- Insufficient funding and support, together with a shortage of epidemiological data and information, are the main issues reported in the field of RDs research. This lack of funding also affects the conduct of clinical trials.
- The main challenge in terms of equity and access to orphan drugs in Spain is the limitations and delays in funding (83%), followed by the disparity of processes between the ACs (73%).
- 47% of stakeholders believe that there are clear differences in access and equity in access to OMPs between regions in Spain, and 80% believe that the current timelines for the overall process of authorisation, evaluation and funding of OMPs are too long.
- According to respondents, greater uncertainty in the measurement of clinical benefit and/or effectiveness (8.8) is the main stumbling block in the authorisation, evaluation and funding process for OMPs, compared to medicines for prevalent diseases, followed by poor timeliness (8.1) and regulatory issues (8.0).

Progress

- 73% of stakeholders identify international collaboration and research networks as the most important element that has been introduced to improve the design and execution of clinical trials in RDs.
- The EMA's special authorisation programmes are considered to be the most important development in terms of access to OMPs, followed by the regulation on availability of medicines in special situations and early access or compassionate use programmes.
- The three most significant developments in the authorisation, evaluation and funding of orphan drugs are the implementation of the Regulation 141/2000 (7.9), the use of broader criteria for drug evaluation and funding (7.8) and the creation of fast-track processes (7.4).
- 67% of respondents indicate that the revision of the procedure and approval of TPRs in Spain, with a specific assessment node for OMPs, has had a positive impact on the efficiency and speed in the assessment of OMPs with respect to medicines for prevalent diseases.

Solutions

- For respondents, the two most important measures to solve the existing challenges in the field of OMPs research are to increase research funding (73%) and to establish public-private partnerships (63%).
- Binding national assessment (7.7), the creation of fast-track processes (7.6) and binding supranational assessment (7.4) are the three most important measures to speed up the assessment and financing process of OMPs.
- 67% of experts considered that economic evaluation should be an important criterion in deciding the price and public funding of a new OMP.
- Half of the respondents consider that cost-effectiveness thresholds for OMPs should be higher than thresholds for other medicines, although there is no consensus on whether they should be used.
- The three fundamental criteria to be considered in drug pricing and financing are the severity, duration and sequelae of the pathologies (8.4), the therapeutic and social value of the drug and its incremental clinical benefit, taking into account its cost-effectiveness (8.3), and the quality of the evidence (8.2).
- A national assessment binding on the ACs and the creation of a national fund could reduce disparities in OMPs access.

Social value

- For respondents, the top three value contributions of OMPs were improving the quality of life of people with RDs (8.1), improving symptoms (7.9) and prolonging the life of people with RDs (7.8).

Conclusions

Due to their rarity and complexity, RDs often present specific challenges in terms of diagnosis and treatment. More than half of all patients with RDs are diagnosed late, resulting in suffering and cost to the system. Therefore, in order to provide high quality, personalised and effective care to patients with RDs, it is necessary to understand the casuistry and differential approach of targeted therapies. Despite the progress made in the last decade, there are still challenges in terms of research, access and regulatory processes that need to be highlighted. In conclusion, the following reflections and considerations are worthwhile in the different areas addressed.

OMPs Research

Although the R&D process for an orphan drug generally follows the same steps as for any other drug, the special nature of orphan drugs means that there are often additional difficulties in getting the drug from conception to marketing.

➜ **What are the challenges?** Patient identification and recruitment may be hampered by the low prevalence and dispersed geographical distribution, especially when dealing with an ultra-rare disease. In addition, the diverse aetiology of RDs poses a challenge in identifying a cohort homogenous enough to participate in a trial. The limited understanding of the natural history of the disease makes it difficult to identify therapeutic targets, define clinical trial objectives and accurately interpret the results obtained. As a result, clinical trials in RDs are costly and time-consuming, making them unattractive to pharmaceutical companies. In addition, there are ethical dilemmas associated with conducting clinical trials and administering experimental treatments to these groups.

➜ **How to address them?** Public and private funding for research should be increased. The promotion of platforms and networks to facilitate the exchange of data and resources between researchers can accelerate drug discovery and development, especially in an international collaborative context. Innovative approaches to clinical trial design are also essential to generate evidence to support regulatory approval. Further investment in the training and specialisation of health professionals in RDs is also needed, as well as raising public awareness of RDs to improve participation in clinical trials.

Access and equity in OMPs

OMPs are often expensive due to low production volumes and high R&D costs, making them difficult to access.

➜ **What are the challenges?** Although current regulations in Spain aim to ensure accessibility and equity in health care, there are significant disparities between autonomous regions in effective access to OMPs, due to the application of different procedures and criteria for authorisation and prescription. In addition, Spain has fewer publicly funded OMPs than other European countries and access times are often longer.

➜ **How to address them?** Advances in equity in access to OMPs must be made at the regulatory and therapeutic levels. Innovative access models are needed to ensure that RDs patients receive the necessary treatments in an expeditious and homogenous manner, regardless of their place of residence. The existence of regional plans for RDs, as well as a greater number of CSUR, the optimisation of the use of RDs registries and greater coverage of national neonatal screening programmes can also help, without forgetting the harmonisation of diagnostic procedures between the different Autonomous Regions to avoid delays.

Regulatory process in OMPs

Given the different characteristics of RDs, implementing a strong regulatory framework plays a crucial role in driving R&D, promoting access to appropriate and equitable treatment, protecting patients' rights and raising public awareness.

➜ **What are the challenges?** In Spain, there is no specific regulation for OMPs, although progress has been made in different areas, such as the approval of the National Strategy and several regional strategies on RDs, the creation of a national registry for RDs, neonatal screening programmes, exemption from the reference price system for OMPs, and greater flexibility in financing these medicines. At the European level, the specific regulation of two decades ago included tax incentives, market exclusivity and specific regulatory support, with a notable impact on the number of OMPs, as well as other aspects, although it needs to be updated. In addition, the new European regulation on health technology assessment, which will be mandatory for OMPs from 2028, poses coordination challenges for its optimal implementation. Added to all this is the regulatory challenge associated with artificial intelligence and the handling of massive data.

➜ **How to address them?** At the national level, it would be desirable to have a national strategy with resources and implemented in a timely and equitable manner across regions. The health technology assessments currently under reform, should be more transparent, independent and participatory, with subsequent dynamic (clinical and economic) reassessment. Pricing should also be more flexible and transparent. At the European level, existing regulatory incentives, such as market exclusivity and specific regulatory advice, should be maintained and even expanded, and coordination between actors and states members in terms of joint clinical assessments should be optimised.

Social value of OMPs

Not only the availability of effective treatments for RDs have a very positive direct impact on patients' health, but these improvements can in turn translate into direct cost savings for the healthcare system as well as indirect cost savings for society, by allowing for greater work productivity and a reduced burden of personal care, resulting in greater societal value.

➜ **What are the challenges?** There is no official definition of what is meant by the social value of innovations, which leads to discrepancies and different interpretations. It is also worth highlighting the limited published evidence on the social value of OMPs , especially with regard to the impact on the burden of personal care and the indirect costs of patients and carers, which is expected to be greater in the case of chronic pathologies or those involving a high degree of physical or mental disability.

➜ **How to address them?** It would be necessary to homogenise the concept of the social value of medicines in general and more particularly for RDs based on societal preferences. Furthermore, it would be necessary to carry out more studies, and in a more cohesive and systematic way, on the effect of OMPs on health outcomes and, above all, on their impact on health costs and indirect costs, avoiding as far as possible conflicts of interest and publication bias.

Opinion of Spanish system stakeholders

This report not only brings together published scientific evidence but also collects first-hand feedback from relevant actors in the system on the challenges and optimal approach to OMPs.

➜ **What are the challenges?** Insufficient funding and support were identified as the most important challenge in the field of OMPs research. Funding constraints and delays were also the main challenge in terms of equity and access to OMPs , followed by regional disparity of processes. Eighty percent of the stakeholders surveyed felt that the current timelines for the overall authorisation, assessment and funding process for OMPs are too long, with the main stumbling block being the increased uncertainty in measuring clinical benefit.

➜ **How to address them?** It would be desirable to increase R&D funding and establish public-private partnerships. The creation of a dedicated national fund and a binding national assessment could reduce disparities in access to OMPs. This, coupled with fast-track processes for OMPs , could also speed up the evaluation and funding process. In addition, economic evaluation should be an important, but not the only, criterion on which to base the pricing and public funding decision for a new orphan drug, allowing in some cases higher efficiency thresholds than for other drugs, especially if there are no therapeutic alternatives or if the disease is very severe. Finally, the therapeutic and social value of the medicine must be taken into account, considering not only the prolongation of patients' lives, but also the improvement of symptoms and quality of life.

INDEX OF FIGURES

INTRODUCTION

CHAPTER 1

CHAPTER 2

CHAPTER 3

CHAPTER 4

CHAPTER 5

TABLE OF CONTENTS

Fundación Weber

aeLmhu