Fundación Weber

International

SUPPLEMENT - NUM 1 - OCTOBER 2023

# newsRARE

Scientific dissemination magazine on Rare Diseases

# RARE DISEASES

## Innovative financing, European funds and best practices

EDITORIAL: Weber Foundation
Moreto, 17 St. 28014 Madrid (Spain)

EDITORIAL COORDINATOR
Irene Barbero
weber@weber.org.es

GRAPHIC DESIGN
Luis de Miguel

NewsRARE is a specialized periodical publication that is mainly distributed to health services organizations. NewsRARE is especially aimed at healthcare professionals, both at hospital level and primary care and public health, who are working in some field related to rare diseases.

ISSN: 2695-8724 (digital version)
Depósito legal: M-31717-2015
doi: https://doi.org/10.37666/R-IN-vol.1-1

newsRARE
SUPPLEMENT | NUM 1 | OCTOBER 2023

# INDEX

# Editorial

## ADDRESSING THE CHALLENGES OF RARE DISEASES: INSIGHTS FROM NEWSRARE

ÁLVARO HIDALGO VEGA

*Editor of newsRARE and President of the Weber Foundation*

Rare diseases represent one of the greatest challenges for medicine, healthcare professionals, national healthcare systems, and especially for the patients who suffer from them.

When we analyze rare diseases from a specific perspective, we understand that the small number of patients with each rare disease hinders scientific progress. It is very complex to develop clinical trials that have the robustness and validity that is standardized in the case of conventional diseases. Furthermore, the absence of alternative treatments in many cases, along with the severe effects on patients' health and quality of life, makes it very difficult to establish control groups in these clinical trials. On the other hand, their infrequency often leads to delayed and complex diagnoses, causing uncertainty and suffering for patients. Similarly, knowledge among healthcare professionals about these types of conditions is often limited and quite specialized. In this sense, if medicine is often a paradigm of specialization, in the case of rare diseases, this specialization is taken to the extreme. For this reason, it is necessary to have reference centers and professional networks that connect experts in each pathology to share knowledge, findings, and experiences. Additionally, the cost of treatments means that approaching them individually for a hospital can generate difficulties and obstacles that can be more easily addressed from a slightly more centralized perspective with a broader view. Finally, if any patient facing an illness needs support and information, in the case of rare diseases, these requirements are multiplied due to the nature of the conditions they suffer from.

This analysis from the particular perspective of each rare disease, valid in each case, may blur the impact and magnitude of the challenge that rare diseases pose for National Healthcare Systems (NHS). Although each rare disease affects a small number of people, to date, between 5,000 and 8,000 have been described, and it is estimated that approximately 30 million Europeans suffer from them in total. The majority are genetic diseases (80%), rare cancers, congenital malformations, autoimmune, toxic, or infectious diseases. However, this categorization is complex due to the wide variety of definitions of what constitutes a rare disease. There are 296 definitions of rare diseases, although in almost all cases, prevalence is used as a criterion for their definition, with the most commonly used range being between 40 and 50 cases per 100,000 inhabitants, with a global average of 40 cases per 100,000 inhabitants.

To date, the European Medicines Agency (EMA) has authorized the marketing of 129 orphan drugs. Around 500 new orphan drugs are in the research phase, and there is already enough information to predict that their budget impact will be around 4-5% of the total pharmaceutical expenditure of Western countries' NHS. Additionally, the high cost per Quality-Adjusted Life Year (QALY) of many of these drugs, along with the high uncertainty about their effectiveness derived from the limitations of their clinical trials, has sparked controversies about the social value of these drugs and poses difficulties in terms of how to finance them and provide access to patients. In this sense, it seems clear that Western societies are willing to pay more for the treatment of these diseases than for more common ones. However, their high opportunity cost and the need to balance efficiency and equity make it necessary to highlight the peculiarities of these diseases and the factors that make their management different, without losing sight of the viability and sustainability of current NHS.

All of these aspects make it necessary to have greater information on both rare diseases and orphan drugs. This was precisely the goal of NewsRARE, the first scientific dissemination magazine in Spain focused on rare diseases. The publication, developed and edited by the Weber Foundation, was created in 2016 with the

aim of generating knowledge and serving as a meeting point and reference for rare diseases and orphan drugs. In general, we publish three issues per year, along with occasional monographic supplements.

The magazine's editorial board includes around twenty healthcare professionals, public managers, and health economists, allowing for a multidisciplinary approach to each of the topics addressed and a clear commitment to action while staying closely connected to the reality of rare diseases and orphan drugs. This is why we have a co-editor, Dr. José Luis Poveda, currently the manager of the University Hospital La Fe in Valencia and one of the leading pharmacists in the world of orphan drugs.

Each issue of the magazine is dedicated to a central topic of special interest related to rare diseases, which is approached from different perspectives to provide relevant and useful information for all levels of involvement: doctors, pharmacists, managers, the pharmaceutical industry, and patients. Over the years, we have delved into the following topics in depth: key aspects of rare diseases in the current environment; clinical evidence of orphan drugs, commercial authorization, and patient registries; economic evaluation and funding of orphan drugs; access to orphan drugs; Multi-Criteria Decision Analysis as an alternative model for evaluating orphan drugs; rare diseases in the time of COVID-19: impact and future prospects; empowering patients with rare diseases and their increasing involvement in decision-making; experiences and health outcomes reported by patients with rare diseases; policies to promote the development of treatments for rare diseases: is it time for an update?; advanced therapies and rare diseases: essential elements for promoting more agile and equitable market access; challenges and impact of artificial intelligence applied to rare diseases; success stories that have transformed the lives and environment of people with rare diseases; funding models for rare diseases: where we come from and where we are going; optimization elements in rare diseases: European funds; value-based healthcare in the field of rare diseases; and neonatal screening and early detection of diseases.

Another relevant section is the newsRARE barometer, which gathers the perception of experts surveyed on the topic at hand. The magazine also offers a range of resources available to professionals and patients, such as reviews of relevant scientific articles, news of interest, or an observatory that presents the evolution of indicators related to rare diseases and therapies aimed at treating them.

One of our main objectives is to be a channel for dissemination that allows us to continue educating and informing patients to increase their active participation in all processes related to very low-prevalence conditions. For this purpose, the interviews section, which captures the experiences and opinions of healthcare professionals, managers, representatives of the pharmaceutical industry, academics, and patients, holds a special place that enables the transmission of knowledge and the exchange of viewpoints from different social agents involved in the management of rare diseases or affected by them. Additionally, the humanization section provides a specific space for the dissemination of healthcare or social initiatives that offer a more humane and patient-centered approach to rare diseases.

For all the reasons mentioned above, and with the firm purpose of providing current, detailed, and rigorous scientific information that is also accessible and approachable, NewsRARE aims to be a communication channel open to anyone interested in rare diseases. NewsRARE is made possible thanks to the sponsorship of leaders in orphan drug innovation who actively collaborate in proposing content and selecting the topics to be addressed in each issue, alongside the magazine's editorial and writing board. For this reason, I would like to express my gratitude to Alexion, Astellas, Boehringer Ingelheim, CSL Behring, CSL Vifor, Chiesi, Jazz Pharmaceuticals, Ipsen, Novartis, Roche, and UCB.

The integration of Weber into the international Vivactis group has offered us the opportunity to expand NewsRARE beyond the Spanish-speaking region (Spain and Latin America). For this reason, in collaboration with HM3A, we have launched this international English-language supplement to disseminate the content of NewsRARE in Europe and the Anglo-Saxon world. The goal for the coming year is to continue with this process of internationalizing the magazine and to publish the magazine in other European countries because we believe it is necessary to continue working for patients with rare diseases. We encourage our new readers to interact with us and to provide us with their suggestions or proposals for collaboration to include their content.

# SUCCESSFUL CASES THAT TRANSFORMED THE LIVES AND ENVIRONMENTS OF PEOPLE LIVING WITH RARE DISEASES

FERNANDO ABDALLA, NÉBOA ZOZAYA
*Department of Health Affairs & Policy Research, Vivactis Weber*

More than 300 million people with rare diseases (RDs) in the world (3 million in Spain)[1], still have problems and challenges. Thirty percent of the 150 million children with RDs worldwide die before their fifth birthday, while for 90% of patients with RDs there are still no specific treatments for their pathology. On the other hand, in Spain, it is estimated that the average time to diagnosis of a RD is 5 years, reaching more than 10 years in 19% of cases[1,2].

If, on the one hand, the recognition of remaining needs motivates human beings to want to continue on the path of development, on the other hand, it is also necessary to recognize the successes that have been achieved. Thus, any action that aims to promote future impro-

vements includes an evaluation of past achievements and results[3].

The advances made in the last twenty years in the field of RDs have brought hope to many people suffering from or living with this type of rare disease through more and better diagnoses, new treatments, the approval of regulatory frameworks, the prioritization of health policy aspects, the creation of support networks, and increased research activity, to name but a few examples[4].

The effort to bring together and publicize some of these success stories can help to raise awareness in society of the need to collectively make further progress in improving the lives and environments of people with RD. In addition, learning about national and international good practices can help to launch similar initiatives in other places and settings.

This is what we seek to do with this article, in which we will first give an overview of the main developments to date in different areas associated with RDs, and then exemplify specific success stories that have changed the history of many patients. We will highlight both initiatives aimed at improving the lives of individuals or families and others aimed at generating change at the national or global level. Finally, we will look to the horizon, with the aim of outlining how and in what ways this progress could continue to take place.

## PANORAMIC VIEW OF PROGRESS

This section gives a broad overview of the main progress made in the last two decades in the field of RDs. These were diseases that were once practically invisible and untreatable, but today, thanks to efforts made in different spheres such as clinical, research, political, and associative, they are not only visible, but are also considered priorities in terms of health and human rights[5].

We have grouped developments around diagnosis, treatment, research, integrated care, use of technology, as well as policy, regulatory, and associative movements (Figure 1).

**The progress achieved in the past two decades in the field of research and development has brought a glimmer of hope to many individuals who suffer from or live with these rare types of pathologies**

Progress in the diagnosis of rare diseases is based on the identification of new RDs and their underlying causes, often of genetic origin, and the development and availability of analytical tests associated with their discovery. It is worth noting that, mainly thanks to the complete DNA sequencing achieved between 2010 and 2020, an average of 260-280 new RDs have been diagnosed each year, and the number of available genetic tests has almost doubled (in 2020, tests were available for 4,200 RDs, compared to 2,300 in 2010). In addition, diagnostic efficiency has increased considerably for patients in the last five years, from 10% to 30-50%[6]. Finally, several initiatives are focused on diagnosing unknown diseases, such as the Undiagnosed Diseases Network (UDN, USA), the Undiagnosed Diseases Programme (UDP, USA), the Undiagnosed Diseases Network International (UDNI) and the Undiagnosed Diseases Programme (ENoD, Spain)[1].

There has also been a notable evolution in the treatments available. Between 2010 and 2023, the European Medicines Agency (EMA) designated 1,892 orphan medicinal products (OMPs) for the treatment of 298 RDs. Another element worth highlighting is the increased focus on drugs approved by this same agency that target RDs. In the period of 1996-2017, these represented only 10% of the total, but in 2018-2020, their share increased to 18.4%, with an average annual number of authorizations of OMPs increasing from 3 to 15[8]. Therapeutic novelties include small molecules, enzyme replacement therapies, antibody immunotherapy, therapeutic proteins, gene therapies, stem cells, regenerative medicine, RNA-based therapies, and nanotechnological advances, among others[1].

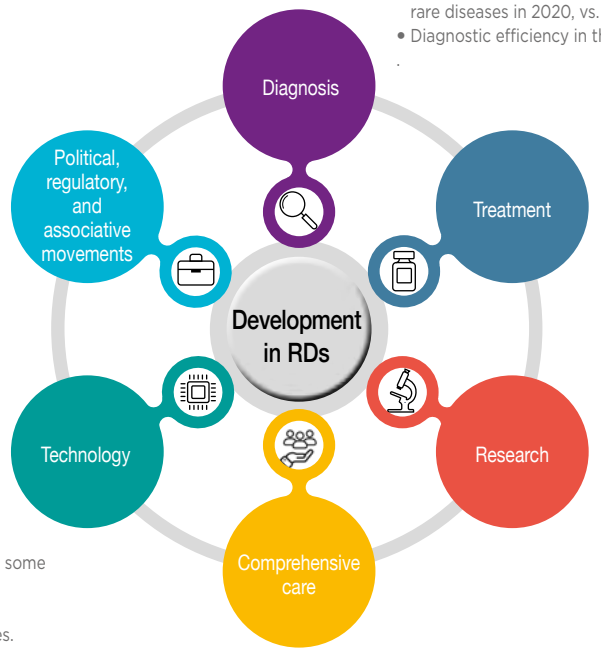
In addition, there has been a surge in research on targeted therapies for RDs. Between 2000 and 2020, a total of 30,029 clinical trials were registered in the world's four largest databases (Europe, the United States, Japan, and China, which contain more than 85% of all global data) for the development of more than 2,000 drugs for the treatment of RDs[12,13]. While between 2000 and 2010, an average of 900 clinical trials were initiated each year for RDs, between 2010 and 2020 this number doubled to 1,800 new studies per year[12,13]. In Spain, as of December 2022, there were 162 clinical trials

FIGURE 1: PROGRESS MADE IN RARE DISEASES UNTIL TODAY

- *The Orphan Drug Act (USA) and the European Regulation as foundations for development.*
- *28 European countries with national strategies.*
- *Spain: National (2009 and 2014) and regional strategies (9 autonomous regions).*
- *EMA approval instruments (accelerated, PRIME, etc.).*
- *Growth of shared risk agreements to improve access.*
- *20% annual growth between 1999 and 2020 in the number of patient associations associated with FEDER.*

- Exponential growth of publications on the use of AI in rare diseases: 200+ between 2010 and 2019, of which 3 in 2010 and 80 in 2019.
- Focus on diagnosis and prognosis.
- Focus on more prevalent rare diseases (55%)

- Implementation of comprehensive care for some rare diseases.
- EU recommendation for the integration of healthcare and social services in rare diseases.
- CSUR: 297, of which 100+ are for rare diseases.




- 260-280 new rare diseases diagnosed each year between 2010 and 2020.
- Double the number of genetic tests available (tests available for 4,200 rare diseases in 2020, vs. 2,300 in 2010).
- Diagnostic efficiency in the last 5 years has increased from 10% to 30-50%.

- Between 2010 and 2023, the EMA has designated 1,892 OMPs for 298 rare diseases.
- The proportion of OMPs approved by the EMA increased from 10% (1996-2017) to 80% (2018-March 2023).
- Average number of OMP authorizations by the EMA: 3 (1996-2017) vs. 14 (2018-March 2023).

- 10% annual increase in the number of clinical trials for therapies targeting rare diseases (2010-2020) globally.
- Success in collaborative research activities (23 RDCRN, 24 ERN, 62 CIBERER groups, etc.).
- Creation of specific registries for rare diseases (highlighting REpIER, Spain-RDR, and ReeR in Spain).

**RDs**: rare diseases. **EMA**: European Medicines Agency. **OMPs**: orphan medicinal products. **RDCRN**: Rare Diseases Clinical Research Network (United States). **ERN**: European Reference Networks. **CIBERER**: Center for Biomedical Research in Rare Diseases Network (Spain). **REpIER**: Rare Diseases Epidemiological Research Network. **Spain-RDR**: Spanish Network of Rare Disease Registries for Research. **ReeR**: State Register of Rare Diseases. **EU**: European Union. **CSUR**: National Health System Reference Centres, Services and Units. **PRIME**: evaluation of EMA priority medicines. **FEDER**: Spanish Federation for Rare Diseases. **CCAA**: Autonomous Communities. **USA**: United States. **AI**: artificial intelligence.

Sources: *Own elaboration based on Groft (2021), Monaco (2022)[1] Monaco (2022)[6], Weber Foundation (2020[7], 2021a[8], 2021b[9], 2021c[10], 2022[11], 2023[12]), Sakate (2018)[12], NIBIOHN (2021)[13], Vicente (2021)[14], Orphanet (2021)[15], Castro (2017)[16], European Commission (2016)[17], Ministry of Health (2021)[18], Posada (2016)[19], EURORDIS (2020)[20], OCDE (2019)[21], FEDER (2020)[22].*

underway for the development of OMPs[9].

Part of the success in research is due to collaborative activities, such as the 23 consortia of the Rare Diseases Clinical Research Network (RDCRN, USA), the 24 European Reference Networks (ERNs), or the 62 research groups of the Centre for Biomedical Research in Rare Diseases Network (CIBERER) in Spain. These increase research capacity through national and international multidisciplinary networks that bring together the strengths and resources of federated platforms related to data collection, exchange, and analysis activities[1]. Another key aspect for the development of research was the creation of specific registries for RDs. In Spain, these include the Epidemiological Network for Research on Rare Diseases (REpIER: 2003-2006 project), the Spanish Network of Rare Diseases Registries for Research (Spain-RDR: 2012-2015) and the State Register of Rare Diseases (ReeR)[14]. These three projects were responsible for the creation of 94% of all regional population-based RD registries in Spain[14]. Currently, Spain has 57 RD registries, of which 39 (68%) are national, 12 (21%) are regional and the rest are European or international (11%)[15].

On the other hand, the coordination and integration of care for patients with RDs is essential, as in most cases, they require the attention and support of different health professionals, social workers, and other professionals involved in the care pathway of these patients[16]. In this regard, although there is no specific data on how many RDs have benefited from the application of integrated care (including health, social, community, and multidiscipli-

nary teams) in the past and present, there are several examples of new care models implemented for RDs, such as hemophilia, cystic fibrosis, and neurofibromatosis, among others[16]. Additionally, it is worth mentioning the unanimous recommendation by the European Commission's ERD Expert Group for the integration of health and social care services in the care of patients with rare diseases in the member states[16,17]. Likewise, in this aspect, it is essential to have units that concentrate specific knowledge and experience in the management of these pathologies. This is the case of the Reference Centres, Services and Units of the National Health System (CSUR). In Spain, there are 297 CSUR[18] of which more than 100 are dedicated to RDs[19].

Also, the use of information and communication technologies, especially related to the application of artificial intelligence to RDs, has grown exponentially. For example, in 2019, 80 scientific articles related to this topic were published, compared to only three in 2010. In this context, the main data sources used were images, demographic data, and omics data, which were mostly applied in models related to diagnostic and prognostic processes. More than half of the publications (55%) referred to diseases with a prevalence of 1-5/10,000 people, and the most frequent diseases investigated were amyotrophic lateral sclerosis, systemic lupus erythematosus, moderate to severe traumatic brain injury, and cystic fibrosis[11].

In the policy space, there has been an enormous effort to establish regulatory frameworks and incentives for the development of treatments targeting RDs. Building on the two main regulatory instruments, the Orphan Drug Act (US, 1983) and the European Regulation 141/2000, many countries, including 28 European countries, have created national plans and strategies for RDs[10,20]. In Spain, apart from the National Strategy on Rare Diseases (RD) published in 2009 and updated in 2014, five Autonomous Regions have approved their own plans, and another four have included specific measures for RD in their health plans[10]. Finally, the implementation of various instruments by the EMA (such as accelerated assessment, priority medicines [PRIME], conditional approval, or approval in exceptional circumstances, among others) has led to accelerated review and approval programs for serious or life-threatening diseases, including many rare diseases and orphan drugs[1].

**The increase in successful cases in the field of RDs leads to many positive changes that make life better for those who have these conditions**

In addition, due to the high costs associated with treatments targeted at rare diseases, a number of alternative financing models have been developed to improve patient access to these treatments. These include risk-sharing arrangements, outcome-based payments, installment payments, and others. According to the OECD, such models are used especially in cancer and other rare disease treatments[21]. In a survey of 14 countries, which asked about the existence of managed drug entry agreements for 104 drugs/indications, approximately 50% were for drugs for RDs or cancer, with 359 agreements (an average of about 3 contracts for each drug/indication)[21].

Furthermore, the role of the advocacy movement is particularly important, as it represents patients in various activities, such as the defense of their rights, raising awareness in society about their problems, and promoting research, among others. In this regard, it is worth highlighting the Spanish Federation for Rare Diseases (FEDER), which acts as the main representative of RD patients in Spain, and its advocacy movement has shown a remarkable evolution over the last twenty years. Between 1999, the year of its constitution, and 2020, the number of members (of which 90% are patient associations) has grown by more than 20% annually, with 380 members at present. In 2003, this network represented 200 diseases, and by 2020, almost 1,200 rare diseases were represented[7,22].

## SUCCESS STORIES THAT CHANGED HISTORY

The emergence of success stories in the field of RDs is often associated with numerous transformations that improve the lives of people affected by these diseases, alleviate the burden on their closest environment, and even achieve significant social benefits. Therefore, it is worth examining some of these success stories and how they have changed history at the individual, family, or societal level.

### Diagnosis and treatment

DDX3X syndrome was first identified in a study conducted in 2015 using a genome sequencing approach.

The study revealed that a gene on the X chromosome called DDX3X was frequently mutated in young girls who had been diagnosed with unexplained developmental delay or intellectual disability[23].

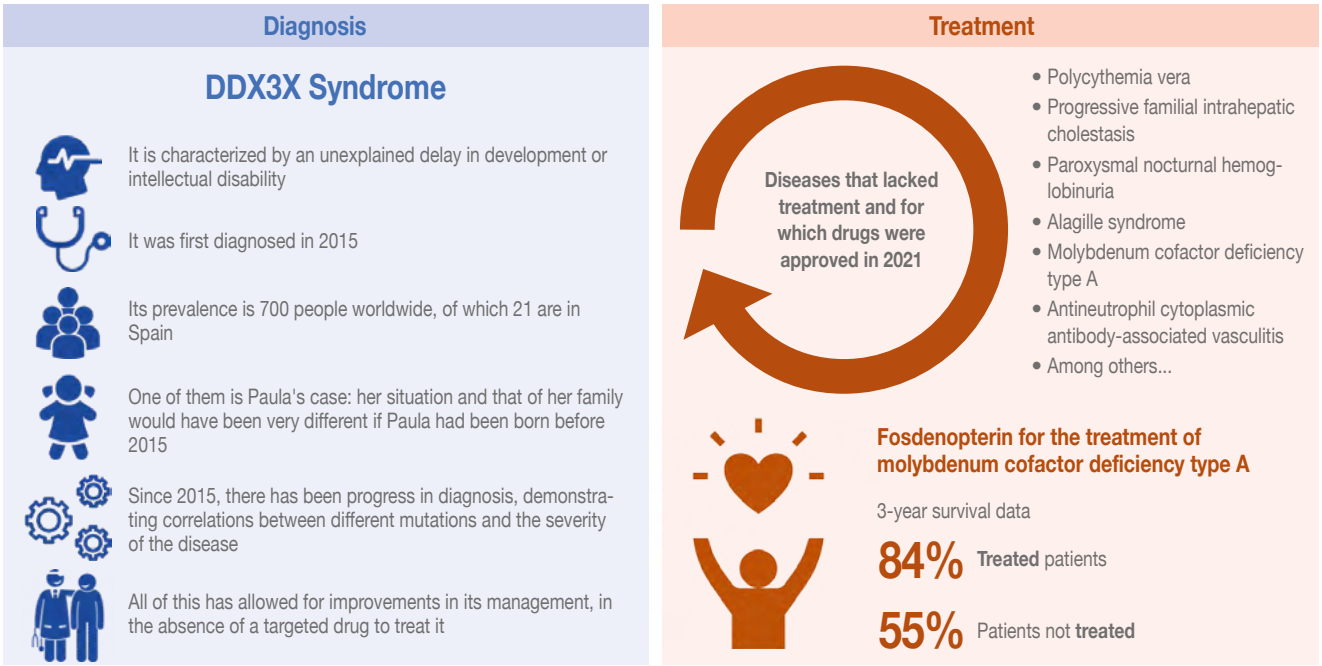
Following this milestone, around 700 cases have been identified worldwide, of which 21 were in Spain. One of them, reported by FEDER, is the case of Paula, a girl born a year after the discovery of this RD. Despite having taken three years to receive a diagnosis, her situation and that of her relatives would undoubtedly have been very different if Paula had been born before 2015[24].

In addition, much progress has been made in understanding mutations in the DDX3X gene. In this regard, the largest cohort study of 107 patients with this disease has been able to demonstrate correlations between different mutations and disease severity[25]. This has led to improvements in its management, which, in the absence of a drug to treat it, is carried out with the aim of improving individual skills, feeding difficulties, behavioral problems, seizures, movement disorders, visual and hearing impairments, and congenital heart defects, among others, through a multidisciplinary approach and psychological support[26].

Although not yet the case for DDX3X syndrome patients, many people benefit from the introduction of new drugs aimed at treating rare diseases with no therapeutic alternatives. As an example, the US Food and Drug Administration (FDA) approved, in 2021, the first targeted drugs for the treatment of rare diseases such as polycythemia vera, progressive familial intrahepatic cholestasis, paroxysmal nocturnal hemoglobinuria, Alagille syndrome, molybdenum cofactor type A deficiency, and antineutrophil cytoplasmic antibody-associated vasculitis, among others[27].

Of particular note is the approval of fosdenopterin in 2021 for the treatment of molybdenum cofactor type A deficiency. Patients with this disease suffer severe and rapidly progressive neurological damage, including intractable seizures, feeding difficulties, and muscle weakness due to the accumulation of toxic sulphite metabolites in the central nervous system. Most patients die in early childhood from infections. Prior to the approval of this drug, the only treatment options were supportive care and therapies aimed at the complications of the disease. After approval, treated patients will have a higher chance of survival (84% at three years, compared to 55% for patients not treated with the drug)[28,29] (Figure 2).

FIGURE 2: SUCCESS STORIES IN THE DIAGNOSIS AND TREATMENT OF RD




Sources: *prepared by the authors based on Álvarez (2020)[23], ERDF (2020)[24], Lennox (2020)[25], Johnson-Kerner (2020)[26], FDA (2021a[27], 2021b[29]) Kang (2021)[28]*

## Research

The research effort is primarily responsible for generating knowledge about the biological basis of RDs, developing new therapies, and making new diagnostic procedures available for these diseases. Cases such as those mentioned above would not be possible without the existence of networks, resources, and people dedicated exclusively to these advances, in order to improve the quality of life of those affected by these pathologies.

Choosing successful cases in this area is a challenge of great magnitude and complexity, given the permanent risk of omitting important and noteworthy milestones. However, it seems essential to mention two examples that introduced major changes in the research field in Spain, such as the Centre for Biomedical Research in Rare Diseases Network (CIBERER) and the State Rare Diseases Registry (ReeR).

CIBERER is a benchmark institution in EERR research in Spain and is part of the *Centro de Investigación Biomédica en Red* (CIBER), a public consortium created in 2006 under the umbrella of the *Instituto de Salud Carlos III*. It is aligned with the objectives of the International Research Consortium on RD (IRDiRC) and has 15 years of experience. Its cooperative network structure, with 62 research groups, and its 7 scientific programs have contributed significantly to the development of scientific production, internationalization, and discovery of new genes and therapies associated with the RDs[30,31].

These successes include the description of over 100 new genes associated with RDs, contribution to the designation of 25 Orphan Medicinal Product Designations (of which 12 were directly sponsored by CIBERER) in Europe and the United States, the diagnosis of 29% of the patients selected for the Undiagnosed Diseases Program (ENoD, Spain), participation in 9 European Reference Networks (ERNs) on different RDs, implementation of 85 intramural projects (with a budget of 4.5 million euros), and the establishment of the Patient Advisory Council (PAC) in collaboration with patient advocacy groups and FEDER. Additionally, the center has received around 8 million euros in funding for research into the genetic aspects of COVID-19[30,31].

**Two notable examples of successful research initiatives in Spain include the *CIBERER* and the State Registry of Rare Diseases**

ReeR, promoted by the REpIER and Spain-RDR projects, and created in 2015 by the Ministry of Health, was one of the first nationwide initiatives for the population-based surveillance of rare diseases. It was created with the aim of providing epidemiological information on RDs in order to promote research on them, increase their visibility, and facilitate adequate health planning and the appropriate distribution of resources. ReeR is composed of all regional RD registries[14]. Its creation has enabled the production of the first national epidemiological report on RDs, which describes the prevalence of 22 RDs in Spain up to 2018. The report includes information on the number of cases (30,378) distributed by Autonomous Community, sex, age group, year of notification, number of deaths, and prevalence per 10,000 inhabitants for each disease (Figure 3)[32].

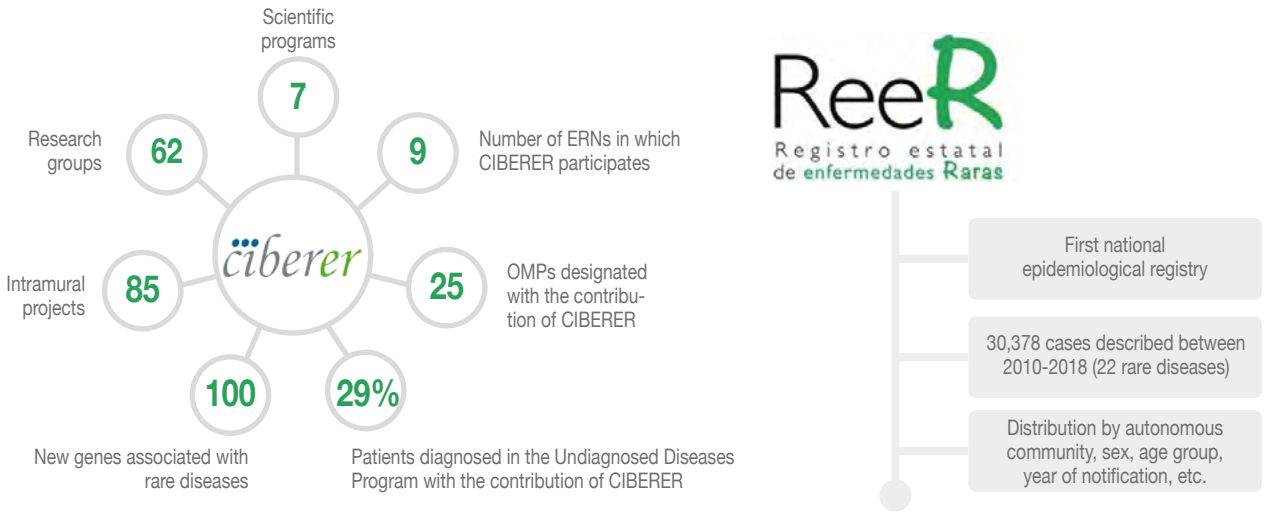
## Integrated care

Bridging the gap between the needs and the care received by patients with RDs in the health, social, and community areas is crucial to increase their life expectancy, quality of life, and autonomy while supporting their basic human rights. In other words, comprehensive care is essential, and various aspects of the care pathway need to be improved[16].

The implementation of a comprehensive care pathway is extremely complex since it requires multidisciplinary teams, the participation and coordination of all actors involved in the process, and a substantial change in perspectives and concepts related to the care and services offered. However, there are several successful initiatives in this field, including the implementation of national standards of care and quality for each medical condition, the establishment of national service and knowledge centers, the creation of networks through bottom-up and consensus approaches, the implementation of case management systems, and the integration of services into one-stop-shop units, among others[16].

A concrete example of success in this area is the PRIOR-ERHR project, which was launched in 2009

FIGURE 3: RESEARCH SUCCESS STORIES




**CIBERER**: Centre for Biomedical Research Network on Rare Diseases. **UDP**: Undiagnosed Diseases Programme. **RDs**: Rare Diseases. **ERN**: European Reference Networks. **OMPs**: Orphan Medicinal Products.

Sources: *Vicente (2021)[14], Luque (2022)[30], CIBER (2022)[31], Ministry of Health 2021)[32]*

in France. The project involved the implementation of a regional case management center for rare diseases, covering 5.6% of the country's population (3.6 million inhabitants, including 180 thousand patients with rare diseases). The center consists of a mobile team of professionals from clinical, genetic, social work, psychology, and occupational therapy, with a coordinated network of 23 institutions. The coordination center provides information to rare disease patients, creates a regional knowledge inventory, directs patients to the most appropriate health and social services, and monitors patients' social and daily life aspects, among other services[16,33]. The results up to 2015 showed that over 750 patients (40% of the total population of people with rare diseases in the region) were attended to, over 30 coordination meetings were held between professional, health, and social institutions, 850 professionals were involved and trained, and 17 unmet needs were identified and categorized[33,34].

**A success story in France is the regional center of case management for RDs, which coordinates a network of 23 institutions**

Telecare can be a useful tool in situations where there are difficulties in accessing health and social care services. This is particularly relevant for rare neuromuscular diseases (RMDs), which have a low prevalence and are geographically dispersed. RMDs are also characterized by a progressive loss of muscle strength, atrophy, fatigue, and other muscle-related symptoms[35]. According to the results of a recently published study in Spain, telecare has led to an improvement in the quality of life of 73 patients who received psychosocial services through seven telematic consultations. The consultations consisted of five blocks, namely psychosocial training, relaxation, emotional reactions, irrational beliefs, and problem-solving. After the implementation of this program, a 7% improvement was detected in the general health status of the participants, as measured by the SF-36 questionnaire (39.42 vs. 41.62 at the end of the sessions), and a 23% improvement in the mastery of emotional limitations (59.16 vs. 72.50)[35].

Additionally, the concentration of knowledge and expertise in CSURs is crucial for the improved care of patients with RDs. Continuing with the example of patients with RMDs, it is worth noting that

there were no CSURs dedicated to these diseases before 2016. Currently, there are seven CSURs located in Catalonia (4), the Community of Madrid, Andalusia, and the Community of Valencia (1 in each)[36]. It is estimated that each year the more than 50 dedicated professionals see 1,150 new patients and follow up a further 4,550 patients (Figure 4)[36].

**The CSUR's wealth of knowledge and experience is indispensable for enhanced patient care. Each year, they provide care to 1,150 new patients with RMDs and additional 4,550**

## Political, regulatory, and advocacy movements

The policy advocacy efforts to date aimed at supporting and providing a regulatory framework for the development of initiatives to improve the lives of people with RDs have been far-reaching and have taken place at all levels (global, national, and regional)[10]. Thus, as in other areas, choosing a single success story related to the policy framework for RDs is a difficult task, as it requires omitting many milestones that transformed the policy history of continents, countries, families, and individuals.

At the same time, this task is facilitated by the fact that these policies continue to be updated and intensified on an ongoing basis. A recent example of this is the UN General Assembly's unanimous adoption of a resolution by its 193 members in December 2021 to address the challenges faced by people living with RDs and their families[37]. This text, which has been in the making for more than five years, represents a historic event and marks a turning point in the global political landscape, as it is now part of the UN Social Development agenda[38]. The resolution calls on Member States to strengthen their health systems to provide universal access to a range of healthcare services, empower people living with RDs to meet their physical and mental health needs, improve equity and equality in health, end discrimination, eliminate gaps in coverage, and create a more inclusive society[37]. The Assembly also urged Member States to implement national measures to ensure that people with RDs are not left behind, recognizing that they are often disproportionately affected by poverty, discrimination, and a lack of decent work and employment[37].

FIGURE 4: SUCCESS STORIES IN INTEGRATED CARE

**PRIOR-ERHR, FRANCE**

- Regional center for case management of rare diseases in France
- 5,6% of the country´s population (3.6 millions inhabitants, 180,000 patients with rare diseases)
- Comprised of a mobile team with professionals from clinical, genetic, social work, psychology, and occupational therapy areas, with a coordinated network between 23 institutions
- 750 patients served (40% of the total population of people with rare dideades in the region)
- More than 30 coordination meetings between professional, health, and social institutions
- 850 professionals involved and trained
- Identification and categorization of 17 unmet needs, among others

**Rare neuromuscular diseases:** low prevalence and high geographical dispersion, are characterized by progresive loss of muscle strength, atrophy, fatigue, and other symptoms related to the musculature

**Teleassistance**

73 patients with this disease received psychosocial services in 7 tele-assistance consultations

- **7%** Improvement in the overall heath status
- **23%** Improvements related to the domain of emotional limitations

**CSUR**

- **0** CSUR units available for this disease before 2016
- **7** CSUR units available for this disease in 2018

Sources: *Castro (2017)[16], Bonneau (2015)[33], Ministry of Solidarity and Health of France (2013)[34], Martínez (2021)[35], Spanish Ministry of Health (2021)[36]*

Moreover, it is essential to highlight the importance of the associative movement in this historic approval, as this resolution was the result of a continuous work of different civil society partners, including the Committee of Non-Governmental Organizations (NGOs) for Rare Diseases, Rare Diseases International (RDI), the European Organization for Rare Diseases (EURORDIS), and national Rare Diseases groups and associations from more than 100 countries, whose leadership at the Spanish level was provided by FEDER[38,39].

Despite the importance of establishing incentivize policies, regulatory frameworks, and associative movements, bringing treatments to all patients requires additional efforts in terms of financing models, in the sense of balancing different aspects, including price, uncertainty in evidence, and huge unmet needs[21].

**In December 2021, the United Nations General Assembly unanimously approved a resolution aimed at addressing the challenges faced by individuals living with a RD and their families**

In this regard, interest in the use of pay-for-performance arrangements to manage the entry of innovative medicines for rare diseases has been increasing over the years, benefiting patients who previously had no therapeutic options[21].

One example is the first drug funded for the treatment of 5q spinal muscular atrophy, a severe, progressive and potentially fatal muscle disease, which will benefit 30 children in Spain[40–42]. The financing of this medicine in Spain was based on a mixed model comprising a pay-for-results agreement and a pay-for-volume agreement. To this end, criteria have been agreed upon related to the expected benefits of the use of this therapy in terms of improvements in motor, respiratory, and bulbar (feeding) function. According to this agreement, children are expected to improve these functions over time progressively until, from the fourth year of treatment administration, they are able to walk and feed themselves without assisted ventilation[40–42] (Figure 5).

## COORDINATED EFFORT TO ACHIEVE AMBITIOUS GOALS

From the 2000s to the present day, we have experienced an unprecedented period of success and joint efforts that have trans-

FIGURE 5: SUCCESS STORIES IN POLITICAL, REGULATORY, AND ASSOCIATIVE MOVEMENTS

**Resolution by the United Nations General Assembly to address the challenges of people living with RDs (December, 2021)**

**193** Members approved it unanimously

**54** Countries co-sponsored it

**5** Years of trajectory until its approval

**Support from the associative movement**

- Committee of Rare Diseases
- Rare Diseases International (RDI)
- European Organization for Rare Diseases (EURORDIS)
- National rare diseases groups and associations from more than **100** countries
- **FEDER: leader in Spain**


Sources: *United Nations (2021)[37], FEDER (2021)[38], International Day for Rare Diseases (2022)[39]*

formed the lives of many patients with RDs, extending to their families and society. Paradoxically, further development in terms of research and diagnosis has led to greater visibility of the magnitude of unmet needs related to treatments, care processes, quality of care, etc.

To ensure that no one is left behind, efforts at all levels must therefore continue to be increased and coordinated[43]. The recent resolution adopted at the UN General Assembly and the recommendations of the Rare2030 project, as well as the review of existing regulatory frameworks such as the European Regulation and the Pharmaceutical Strategy contribute to this. New approaches to address the problem of undiagnosed genetic diseases and the pipeline of more than 550 drugs in development for the treatment of rare diseases are also essential on the path towards closing the existing gaps[44,45].

It remains to be seen whether the efforts made will be sufficient to achieve the proposed targets for the next 10-20 years. To mention just a few, for IRDiRC, one of the targets for 2027 is that "all patients presenting for care with a suspected RD will receive their diagnosis within 1 year if their disorder is known in the medical literature; and that all currently undiagnosed individuals will enter a globally coordinated process related to diagnosis and investigation of their disease"[43].

In addition, one of the recommendations of Rare2030 is to reduce by one-third the level of psychological, social, and economic vulnerability of patients with RDs and their relatives. This is because 7 out of 10 patients have to reduce their professional activity, two-thirds of caregivers spend more than 2 hours caring for patients, and the levels of depression in people with RDs and their relatives are three times higher than those of people without any disease[5].

**A coordinated effort is essential to achieve ambitious future-oriented goals, such as expediting diagnoses to less than a year and reducing by one third the psychological, social, and economic vulnerability of patients**

In conclusion, much has been achieved, transforming the lives of many people, the policies of many countries, and raising awareness of its importance globally. Nevertheless, efforts must continue and be amplified in a cohesive manner, taking advantage of the growing scientific knowledge and the possibilities offered by new technologies, so that the proposed goals are met, and solutions to the remaining challenges are provided, with results that are not only more effective but also benefit as many people as possible.

1. Groft SC, Posada M, Taruscio D. Progress, challenges and global approaches to rare diseases. Acta Paediatr Oslo Nor 1992. 2021;110(10):2711-6, doi: 10.1111/apa.15974.

2. FEDER. Estudio sobre situacion de Necesidades Sociosanitarias Personas con Enfermedades-Raras-en Espana. Estudio ENSERio II. 2018, Available from: https://enfermedades-raras.org/images/pdf/FINAL-ENSERio_Estudio-sobre-situacion%20de-Necesidades-Sociosanitarias-Personas-con-Enfermedades-Raras-en-Espana.pdf.

3. Naranjo Pereira ML. Motivación: Perspectivas Teóricas Y Algunas Consideraciones De Su Importancia En El Ámbito Educativo. Rev Educ. 2009;33(2):153-70.

4. EURORDIS European Organisation for Rare Diseases. 20 Years of Achievements in the Rare Disease Community. 2017.

5. Kole A, Hedley V, Rath A, Rodwell C, Sangiorgi L, Scarpa M, et al. Recommendations from the Rare 2030 Foresight Study: The future of rare diseases starts today. 2021.

6. Monaco L, Zanello G, Baynam G, Jonker AH, Julkowska D, Hartman AL, et al. Research on rare diseases: ten years of progress and challenges at IRDiRC. Nat Rev Drug Discov. 2022, doi: 10.1038/d41573-022-00019-z.

7. Fundación Weber. El empoderamiento de los pacientes con enfermedades raras y su creciente incorporación en la toma de decisiones. NewsRARE, Vol 5 - Núm 2. 2020.

8. Fundación Weber. El valor del medicamento desde una perspectiva social. Madrid, España. 2021.

9. Fundación Weber. Observatorio. NewsRARE. 2021, Available from: https://newsrare.es/observatorio/.

10. Fundación Weber. Políticas de fomento al desarrollo de tratamientos dirigidos a enfermedades raras: ¿es el momento de su actualización? NewsRARE, Vol 6 - Núm 1. 2021.

11. Fundación Weber. Desafíos e impacto de la inteligencia artificial aplicada a las enfermedades raras. NewsRARE, Vol 6 - Núm 3. 2022.

12. Sakate R, Fukagawa A, Takagaki Y, Okura H, Matsuyama A. Trends of Clinical Trials for Drug Development in Rare Diseases. Curr Clin Pharmacol. 2018;13(3):199-208, doi: 10.2174/1574884713666180604081349.

13. National Institutes of Biomedical Innovation, Health and Nutrition (NIBIOHN). DDrare: Database of Drug Development for Rare Diseases. Center for Rare Disease Research. 2021, Available from: https://ddrare.nibiohn.go.jp/cgi-bin/clinical_trials_e.cgi?db=disease_who.

14. Vicente E, Ardanaz E, Ramalle-Gómara E, Echevarría LJ, Mira MP, Chalco-Orrego JP, et al. [Surveillance of rare diseases in Spain: Spanish Registry of Rare Diseases (ReeR).]. Rev Esp Salud Publica. 2021;95:e202111186.

15. Orphanet. Rare Disease Registries in Europe. 2021.

16. Castro R, Senecat J, de Chalendar M, Vajda I, Dan D, Boncz B. Bridging the Gap between Health and Social Care for Rare Diseases: Key Issues and Innovative Solutions. En: Posada de la Paz M, Taruscio D, Groft SC, editores. Rare Diseases Epidemiology: Update and Overview. Cham: Springer International Publishing; 2017. p. 605-27.

17. Commission Expert Group on Rare Diseases. Recommendations to support the incorporation of rare diseases into social services and policies. European Commission. 2016.

18. Ministerio de Sanidad. Hospitales, camas en funcionamiento y puestos de hospital de día (PHD) del Sistema Nacional de Salud (SNS), número y tasa por 1.000 habitantes y número de Centros, Servicios y Unidades de referencia (CSUR) según comunidad autónoma. Portal Estadístico del SNS. 2021, Available from: https://www.sanidad.gob.es/estadEstudios/sanidadDatos/tablas/tabla22.htm.



19. Posada de la Paz M, Alonso V, Bermejo E. Enfermedades raras. Colección Más que Salud; Instituto de Salud Carlos III; Los Libros de la Catarata. ISBN: 978-84-9097-224-3; 2016.

20. EURORDIS. Rare disease plans and strategies in European countries. 2020, Available from: *https://www.eurordis.org/content/rare-disease-plan-and-strategies-european-countries*.

21. OCDE. Performance-based managed entry agreements for new medicines in OECD countries and EU member states: How they work and possible improvements going forward. 2019.

22. Federación Española de Enfermedades Raras (FEDER). Memoria Anual de Resultados. 2020, Available from: *https://enfermedades-raras.org/images/pdf/MEMORIA_FEDER_2020_final.pdf*.

23. Álvarez J. Scientists Unravel Mystery of Rare Genetic Disorder that Causes Intellectual Disability in Females. University of California, San Francisco. 2020, Available from: *https://www.ucsf.edu/news/2020/03/416816/scientists-unravel-mystery-rare-genetic-disorder-causes-intellectual-disability*.

24. Federación Española de Enfermedades Raras (FEDER). Hace tan sólo 7 años que se diagnosticó por primera vez la enfermedad de Paula. 2022, Available from: *https://www.enfermedades-raras.org/index.php/actualidad/16355-hace-tan*-sólo-7-años-que-se-diagnosticó-por-primera-vez-la-enfermedad-de-paula.

25. Lennox AL, Hoye ML, Jiang R, Johnson-Kerner BL, Suit LA, Venkataramanan S, et al. Pathogenic DDX3X Mutations Impair RNA Metabolism and Neurogenesis during Fetal Cortical Development. Neuron. 2020;106(3):404-420.e8, doi: 10.1016/j.neuron.2020.01.042.

26. Johnson-Kerner B, Blok LS, Suit L, Thomas J, Kleefstra T, Sherr EH. DDX3X-Related Neurodevelopmental Disorder. University of Washington, Seattle; 2020.

27. FDA. New Drug Therapy Approvals 2021. 2021.

28. Kang C. Fosdenopterin: First Approval. Drugs. 2021;81(8):953-6, doi: 10.1007/s40265-021-01520-2.

29. FDA. FDA Approves First Treatment for Molybdenum Cofactor Deficiency Type A. 2021, Available from: *https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-molybdenum-cofactor-deficiency-type*.

30. Luque J, Mendes I, Gómez B, Morte B, López de Heredia M, Herreras E, et al. CIBERER: Spanish national network for research on rare diseases: A highly productive collaborative initiative. Clin Genet. 2022, doi: 10.1111/cge.14113.

31. CIBER. Un estudio publicado en 'Clinical Genetics' destaca el éxito del modelo de investigación en red del CIBERER. 2022, Available from: *https://www.ciberer.es/noticias/un-estudio-publicado-en-clinical-genetics-destaca-el-exito-del-modelo-de-investigacion-en-red-del-ciberer*.

32. Ministerio de Sanidad. Informe ReeR 2021: Situación de las Enfermedades Raras en 2010-2018. 2021.

33. Bonneau D. PRIOR-RH. A Regional Centre for People Living with Rare Diseases. Department of Genetics, University of Angers, France. 2015.

34. Ministére des Solidaritès et de la Santè. PRIOR Maladies Rares, un partenariat entre centres experts et associations. 2013, Available from: *https://solidarites-sante.gouv.fr/systeme-de-sante-et-medico-social/parcours-de-sante-vos-droits/bonnes-pratiques-en-region/pays-de-la-loire/article/prior-maladies-rares-un-partenariat-entre-centres-experts-et-associations*.

35. Martínez O, Amayra I, López-Paz JF, Lázaro E, Caballero P, García I, et al. Effects of Teleassistance on the Quality of Life of People With Rare Neuromuscular Diseases According to Their Degree of Disability. Front Psychol. 2021;12:637413, doi: 10.3389/fpsyg.2021.637413.

36. Ministerio de Sanidad. Relación de centros, servicios y unidades de referencia (CSUR) del sistema nacional de salud designados para la atención o realización de las patologías o procedimientos que se indican. 2021, Available from: https://www.sanidad.gob.es/profesionales/CentrosDeReferencia/docs/ListaCSUR.pdf.

37. United Nations. General Assembly Adopts 59 Third Committee Texts on Trafficking in Persons, Equitable Access to COVID-19 Vaccines. Meetings Coverage and Press Releases. 2021, Available from: https://www.un.org/press/en/2021/ga12396.doc.htm.

38. Federación Española de Enfermedades Raras (FEDER). La Asamblea General de Naciones Unidas adopta la resolución enfocada a personas con enfermedades raras. 2021, Available from: http://enfermedades-raras.org/actualidad/noticias/%C2%A1cuenta-atras-para-la-adopcion-de-la-resolucion-de-la-onu-sobre-enfermedades-raras-2.

39. Rare Disease Day 2022. Resolution for People Living with a Rare Disease adopted by the United Nations. 2021, Available from: https://www.rarediseaseday.org/news/resolution-for-people-living-with-a-rare-disease-adopted-by-the-united-nations/.

40. La Moncloa. Los niños con Atrofia Muscular Espinal (AME) contarán con un nuevo tratamiento de terapia génica incluido en el SNS. 2021, Available from: https://www.lamoncloa.gob.es/serviciosdeprensa/notasprensa/sanidad14/Paginas/2021/011221-terapiaame.aspx.

41. Ministerio de Sanidad. Acuerdos de la reunión de la Comisión Interministerial de Precios de los Medicamentos. Sesión 211 de 7 de abril. 2021, Available from: https://www.sanidad.gob.es/profesionales/farmacia/pdf/ACUERDOS_DE_LA_CIPM_2112_web.pdf.

42. Ministerio de Sanidad. Acuerdos de la reunión de la Comisión Interministerial de Precios de los Medicamentos. Sesión 217 del 28 de octubre. 2021, Available from: https://www.sanidad.gob.es/profesionales/farmacia/pdf/ACUERDOS_DE_LA_CIPM_217_web.pdf.

43. Austin CP, Cutillo CM, Lau LPL, Jonker AH, Rath A, Julkowska D, et al. Future of Rare Diseases Research 2017-2027: An IRDiRC Perspective. Clin Transl Sci. 2018;11(1):21-7, doi: 10.1111/cts.12500.

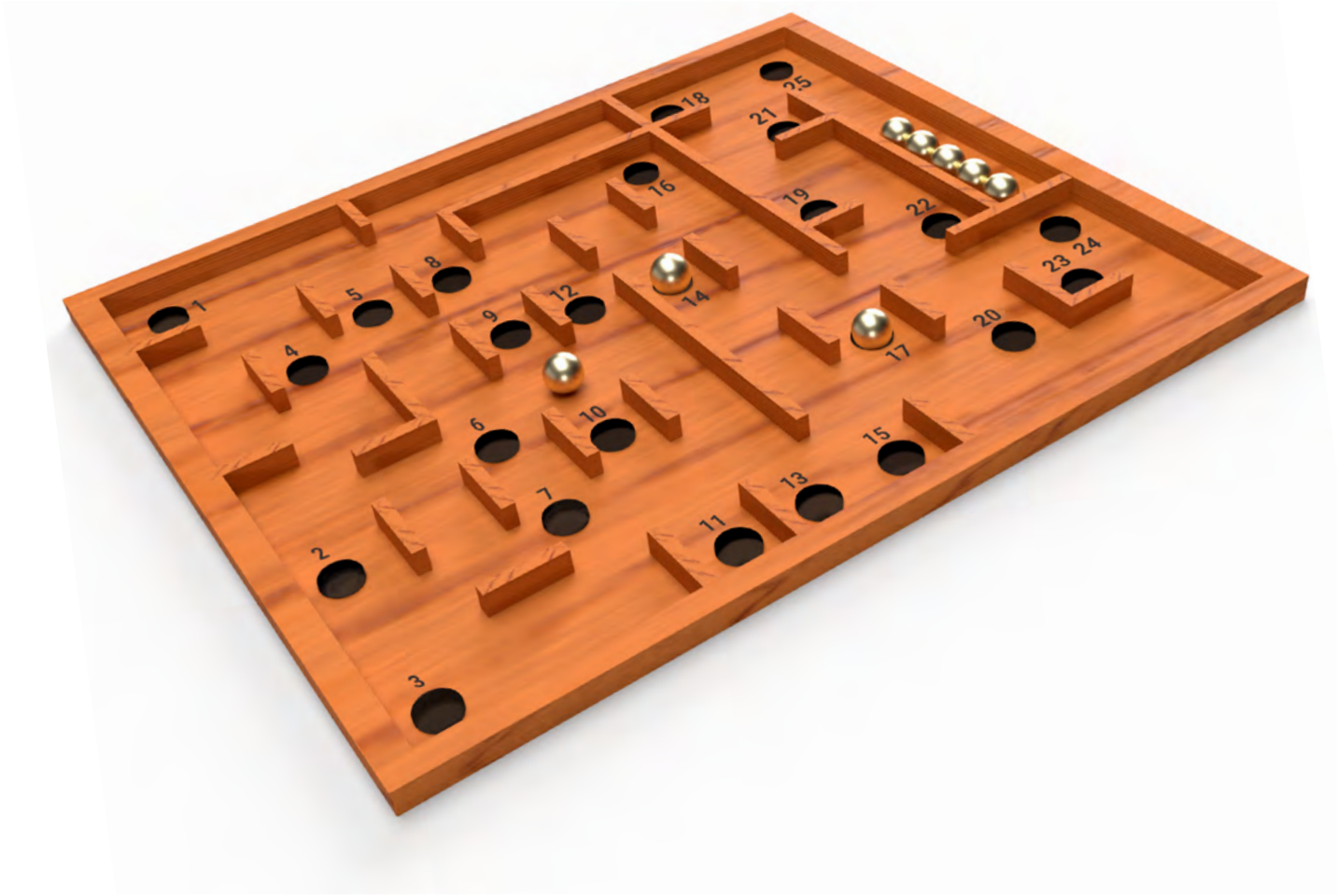
44. Hartley T, Lemire G, Kernohan KD, Howley HE, Adams DR, Boycott KM. New Diagnostic Approaches for Undiagnosed Rare Genetic Diseases. Annu Rev Genomics Hum Genet. 2020;21:351-72, doi: 10.1146/annurev-genom-083118-015345.

45. PhRMA. Progress in Fighting Rare Diseases. 2021, Available from: https://phrma.org/resource-center/progress-in-fighting-rare-diseases.

# INNOVATIVE FUNDING MODELS IN THE FIELD OF RARE DISEASES: WHERE WE COME FROM AND WHERE WE ARE GOING

CARLOS DÉVORA, FERNANDO ABDALLA, NÉBOA ZOZAYA

*Department of Health Economics & Market Access, and Health Affairs & Policy Research, Vivactis Weber*



Health technology funding decision processes, in general, and more specifically, for medicines aimed at the treatment of rare diseases (RD), carry a certain degree of risk for health authorities. This is due to the absence of "perfect" information on several relevant aspects, such as the resulting final budgetary impact or real life-effectiveness, partly due to the greater uncertainty associated with this type of medicines, due to the greater difficulty in conducting clinical trials and generating solid evidence in a standard period of time[1,2].

Furthermore, the risk associated with the introduction of a medicine for a rare disease is not only borne by the payer, but the pharmaceutical company also faces uncertain-

ties about public reimbursement, timelines, pricing and the volume of product demanded, hence both parties have incentives to agree on risk-reducing financing formulas[1,3].

Traditionally, the financing of these medicines was based on the establishment of maximum prices for each product, considering aspects such as therapeutic benefit, the target population, the existence of alternatives or the degree of innovation, among others. However, in order to address the existing uncertainties, in recent years some countries have introduced innovative financing models in the field of RDs, as mechanisms to link the financing of these medicines (especially those with higher costs) to the results obtained, whether financial or in terms of improvements in health[1–3].

The aim of this article is to review the implementation of novel financing schemes to incorporate therapeutic innovation of medicines for RDs in the Spanish National Health System (NHS). To do so, we will describe the main types of existing models in the literature, highlighting their advantages and disadvantages, and then we will exemplify their use in the field of RDs in Spain and Europe. We will also give examples of their application in the field of advanced therapies. Finally, we will analyze the requirements for their implementation and suggest some proposals to reduce the existing barriers to their implementation.

## TYPES OF MODELS, ADVANTAGES AND DISADVANTAGES

Innovative financing models can be divided into two main groups: those based on financial outcomes and those based on health outcomes. In both cases, the objective is to reduce the uncertainty intrinsic to the financing processes, although each type of model aims to mitigate risks of a different nature. Thus, while financial outcome-based models are mechanisms to reduce the uncertainty linked to the budgetary impact of the acquisition of the health innovation, health outcome-based models aim to reduce uncertainty about the effectiveness and cost-effectiveness of these medicines (Figure 1)[1,4].

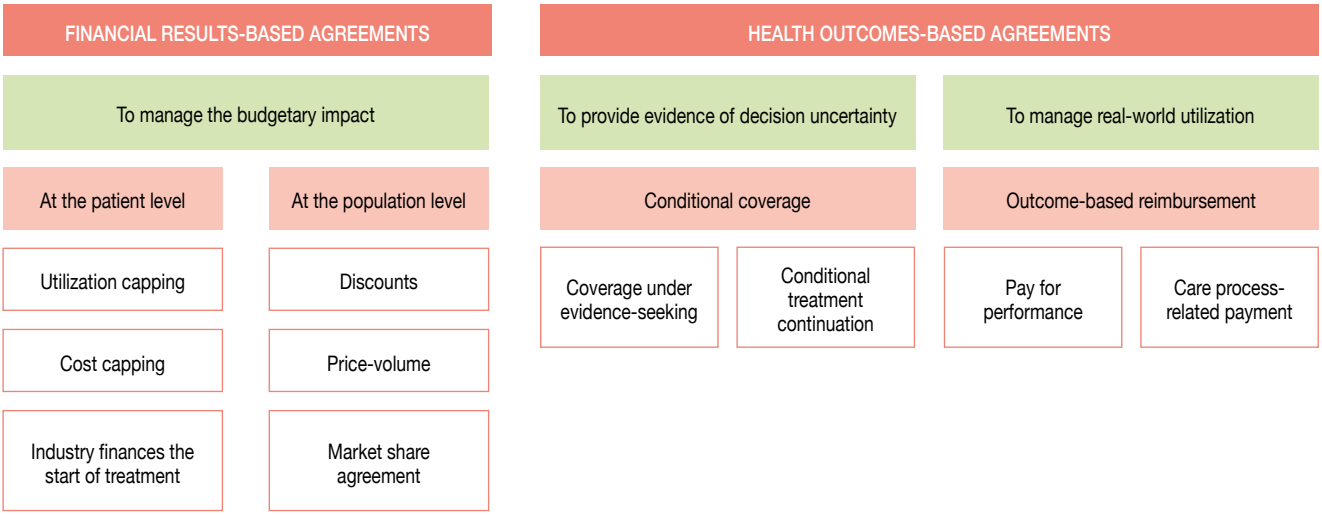
### Models based on financial results

Financial performance-based models are commercial contracts that aim to reduce uncertainties related to the budgetary impact. The main types of agreements in this category are described below[1,4,5].

- **Price-volume**: These agreements link the price of a medication with its volume of sales, usually by offering a lower unit price for a higher volume of sales. These agreements incentivize manufacturers to not increase their sales beyond what is reasonable, or to ensure that the medication is prescribed only for its approved indications.

- **Discounts**: These agreements involve the manufacturer offe-

FIGURE 1: TYPES OF INNOVATIVE FINANCING MODELS




Source: *own elaboration based on Garrison (2013)[4] and Carlson (2010)[5]*

ring discounts to the payer on the cost per patient or providing cash back or free delivery of the medication. These models can help to make funding available for medications that would otherwise be excluded from funding due to their high cost.

- **Budget/cost-capping or utilization/dose-capping**: These agreements set a limit on the total cumulative cost or on the utilization of the medication. If these limits are exceeded, the manufacturer may bear all or part of the cost of the treatment. This helps ensure that the actual budgetary impact does not exceed what was initially anticipated by the payer.

- **Treatment initiation agreements**: The manufacturer pays for all or part of the costs of the initial treatment cycle prior to funding the treatment, pending sufficient evidence (efficacy or effectiveness) to convince the payer that their product is worth funding.

- **Market-share agreements**: They are defined by the establishment of a reduced price when the product is first introduced to the market. By doing so, the supplier aims to increase its market share.

## Health outcomes-based models

Health outcomes-based models are those whereby payment for the medicine is based on the effect on clinical or cost-effectiveness outcomes in actual clinical practice. The main types of arrangements are as follows[1,4,5]:

- **Payment by results**: In this type of agreement, the manufacturer makes refunds or price adjustments if its medicine does not meet the initially agreed health outcomes. These outcomes can be measured in terms of final clinical outcomes (mortality, quality of life, etc.), intermediate outcomes (progression-free survival, biomarkers, etc.) or cost-effectiveness (cost per quality-adjusted life year, etc.).

- **Coverage under evidence-seeking**: The funder is responsible for the payment of the medicine conditional on the manufacturer conducting a scientific study that allows for the collection of additional evidence to corroborate its benefits in real practice. In the case of a clinical trial, payment is made to the trial population. In the case of a larger-scale observational study, payment is made to the entire target population, regardless of whether or not they participated in the study.

- **Conditional continuation of treatment**: For each patient, the payer decides to maintain or withdraw coverage of the medicine based on the level of achievement of a set of short-term clinical outcomes. This ensures that only patients who actually benefit from the treatment will continue to receive it.

- **Payment linked to the process of care**: Under this type of arrangement, the cost of the technology (e.g. diagnostic test) is reimbursed according to the impact it has on the process of care (e.g. if the use of this test allows the reduction of unnecessary treatments). This type of agreement is used more for health technologies than for medicines.

## Advantages and disadvantages

Innovative funding models are associated to certain advantages. Provided they are well managed, they can benefit all stakeholders: (i) for funders: reduction of uncertainty, optimization of resource allocation, greater efficiency in actual clinical practice; (ii) for the pharmaceutical industry: increased market access and return on investment, real improvement in effectiveness (incentives for continuous product improvement); (iii) for healthcare professionals: availability of a protocolized agreement based on clinical indicators, allowing the collection of only relevant data; correct selection of patients who need the medicine; (iv) for patients: greater availability of a protocolized agreement based on clinical indicators, allowing the collection of only relevant data; correct selection of patients who need the medicine; and (v) for patients: increased access to high-priced treatments, better monitoring of clinical outcomes, and faster access[1,3].

However, there is also evidence of risks and limitations in implementing such models. On the one hand, these arrangements may entail excessive bureaucratic burdens and administrative costs in the first phase, as well as high resources for monitoring and evaluation at a later stage. In addition, their implementation generally requires strong information systems that allow for reliable monitoring of the results achieved. Also, the company commerciali-

zing the innovation may increase prices pending the conclusion of such agreements with the funder, which would make such schemes unattractive. Finally, such contracts may give rise to confidentiality issues due to the need to handle and transfer patients' personal data[1,3].

However, there is also evidence of the risks and limitations when implementing such models. On one hand, these agreements can entail excessive bureaucratic burdens and administrative costs in the initial phase, as well as significant resources allocated for their monitoring and evaluation in a later stage. Additionally, their deployment typically requires the existence of robust information systems that enable reliable tracking of the obtained results. Furthermore, the innovation-providing company may adjust prices upward in anticipation of entering into these agreements with the funding entity, which could reduce the attractiveness of these schemes. Finally, these contracts can lead to confidentiality issues due to the necessity of handling and transferring patients' personal data[1,3].

## USE OF ALTERNATIVE FINANCING MODELS FOR RARE DISEASES IN EUROPE

Given the low frequency of RDs[6], orphan drugs (ODs) generally enter the market with limited clinical evidence due to the low number of patients, and at high prices that do not meet standard cost-effectiveness criteria[7]. Some studies estimate that by 2024 the cost of ODs could reach $242 billion, representing one-fifth of global drug sales, with an annual growth rate of 12.3% between 2019 and 2024, which is roughly twice that forecast for the non-orphan drug market[8].

In this context, ODs are considered ideal candidates for applying innovative financing models, thus allowing for greater efficiency of healthcare systems, especially when negotiations occur at an early stage[1,3].

**If well managed, innovative financing models can benefit all stakeholders involved**

In recent years, the proportion of public spending allocated to ODs has increased in most European countries, which has sparked a great interest in agreeing on new reimbursement criteria and conditions, mainly based on economic and efficiency issues[10]. A review carried out by Morel et al. in 2013, which identified 42 risk-sharing agreements (RSAs) for 26 ODs implemented between 2006 and 2012 in five European countries (Belgium, Italy, the Netherlands, Sweden, and the United Kingdom), found that 55% of these agreements were based on health outcomes, mostly in the form of coverage with evidence development. On the other hand, among the agreements based on financial outcomes, discounts were the most frequently used form (approximately 70%). Italy had the highest number of agreements of this type, followed by the Netherlands and England, and oncologic drugs were the main targets of the RSAs[11].

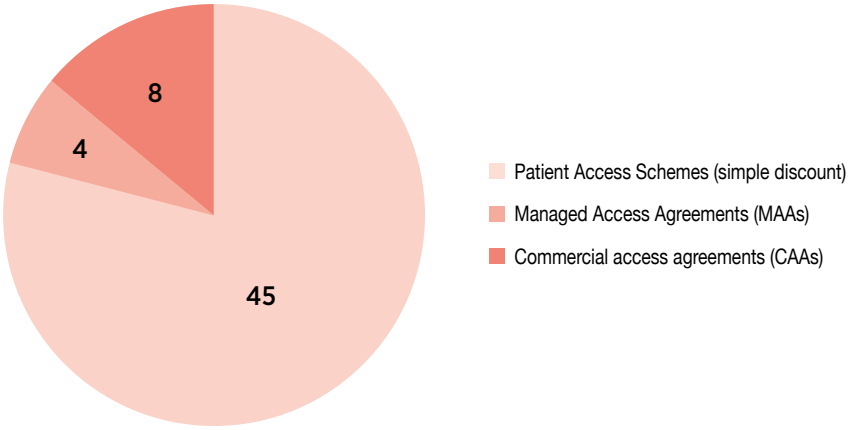
However, nowadays, the information regarding these new financing approaches in the context of ODs is limited. Regarding the accumulated experience and transparency of the results obtained, the information provided in Australia, England, and Italy should be positively highlighted[12].

The experience of the British NHS is perhaps one of the best documented, with funding schemes equivalent to RSAs called Patient Access Schemes (PAS). As of 2021, the NHS had 329 funding agreements in place for mostly oncology medicines, of which at least 57 were with orphan drugs, accounting for approximately one-fifth of the total[13] (Figure 2).

The vast majority of these are simple agreements consisting of applying a discount on the unit cost per patient, thus aligning with the recommendations of the National Institute for Health and Care Excellence (NICE). This has enabled the financing of very recent drugs such as fenfluramine (Fintepla®) for the treatment of seizures associated with Dravet syndrome in children aged 2 years and older, and imlifidase (Idefirix®) for the desensitization treatment prior to kidney transplantation in people with chronic kidney disease[13].

Others, however, access the NHS through more complex funding schemes, such as Managed Access Agreements (MAA), which allow a medicine to be made available for a limited period of time at a discounted price while

FIGURE 2. NUMBER OF ORPHAN DRUGS FUNDING AGREEMENTS IN THE UK UP TO 2021 (N=57)




Source: *prepared by the authors based on NICE*[13]

more data is gathered on its effectiveness in real-world practice; or Commercial Access Agreements (CAA), which enhance the value proposition of a medicine and can be addedd to a simple discount. An example of such an agreement is nusinersen (Spinraza®), indicated for the treatment of 5q spinal muscular atrophy, for which the agreement will run for 5 years, from 24 July 2019 (when the agreement was signed) until 23 July 2024, with a data collection period of at least 3 years[13,14] which will address long-term uncertainties [15].In any case, the NHS reports that the utilization of such agreements in the field of ODs is very widespread, and that they have saved the NHS nearly £196 million between 2019 and 2020[16].

Another example of RSA implementation is Italy, with a powerful system of national registries managed by the Italian Medicines Agency (AIFA)[17,18]. In this country, the first RSA for ODs was signed in 2006, and by 2012, 24 such agreements were already in place, mostly for ODs in the area of oncology[17]. In this respect, Xoxi et al. (2021)[17] have carried out an analysis of AIFA indication-based registrations and associated information from the European Medicines Agency (EMA) over a 15-year period (2005-2019), assessing their characteristics and comparing ODs against other medicines for both oncology and non-oncology indications[17].

**The high uncertainty, together with the high price of orphan drugs, tends to promote the use of risk-sharing agreements**

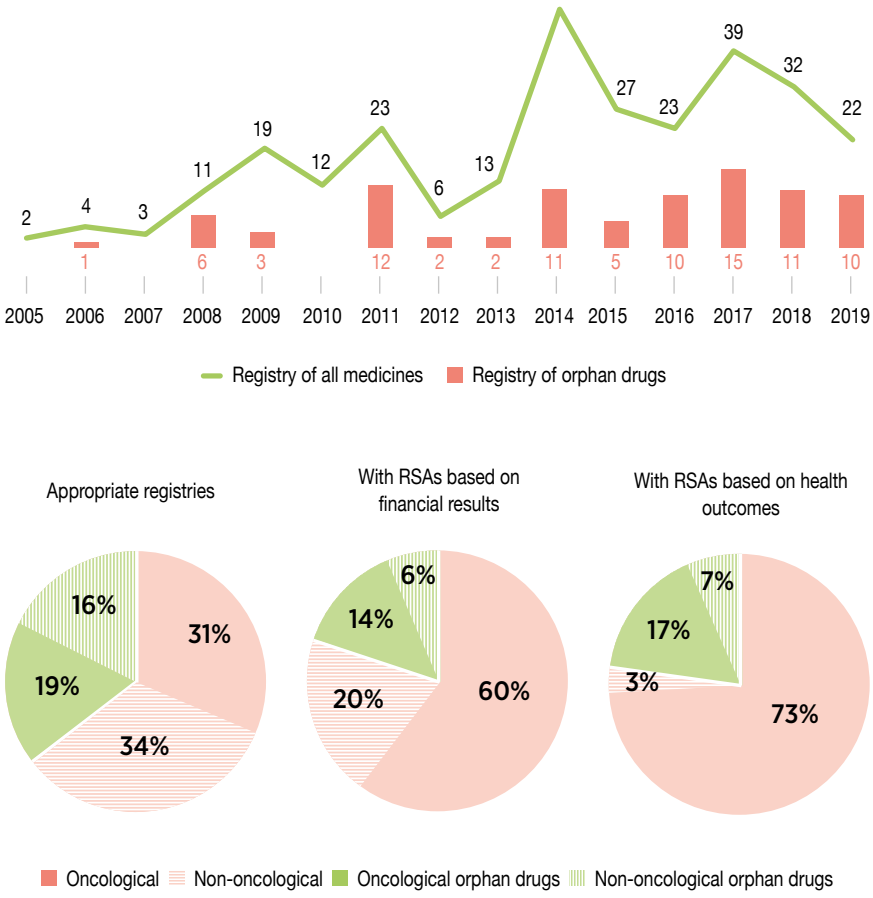
According to their analysis, out of the 283 existing records, 182 correspond to suitability records (35.2% referring to ODs, with a very similar distribution between oncology and non-oncology), 35 include agreements based on financial results (with 20% referring to ODs, 2 non-oncology, and 5 oncology), and 60 refer to payment by results agreements (23.3% corresponding to ODs, 4 non-oncology, and 10 oncology)[16] (Figure 3).

In addition, in Italy there are two types of outcome-based RSAs: Payment by Results (PbR), which provides for reimbursement of 100% of the cost of the drug for responding patients (which in practice has allowed reimbursement of drugs such as Adcetris®, Blincyto®, and Holoclar®, among others); and Payment at Result (PaR), which involves reimbursement only when the treatment is successful, after starting with a free supply or an upfront payment (to which very novel therapies, such as Kymriah and Yescarta, have subscribed)[17].

In the rest of Europe, innovative financing approaches have also been applied in ODs, although detailed information is limited. For example, in France, since 2008, specific agreements with clawback mechanisms above agreed levels have been applied to ODs, with eculizumab (Soliris®) and galsulfase (Naglazyme®) being the first drugs to benefit from this (interestingly, Naglazyme® has lost the ODs designation)[18].

Despite the lack of available information, it is clear that the high uncertainty, together with the high price of ODs tends to promote the use of RSAs. The most recent example is the treatment of metachromatic leukodystrophy with a drug on the market, Libmeldy® (atidarsagen autotemcel), which has a price tag of around 2.5-3 million euros per patient. Countries such as Germany, Italy, and the United Kingdom have

FIGURE 3. EVOLUTION IN THE IMPLEMENTATION OF RISK-SHARING AGREEMENTS IN ITALY, 2005-2019




Abbreviations: **RSA:** Risk-sharing agreement
Source: *Xoxi (2021)*[17]

signed funding agreements recognizing the real efficacy of the drug. In Germany, for example, a purchase price of 2.48 million euros per child has been negotiated, according to information from the laboratory itself[19].

## THE CASE OF ADVANCED THERAPY MEDICINAL PRODUCTS

Advanced therapy medicinal products (ATMPs) serve as a paradigmatic example of how RSAs can ensure access to innovative therapies with high costs and uncertainty about their effectiveness. They are an emerging class of medicines based on genes (gene therapy), tissues (tissue therapy), or cells (cell therapy) that have the potential to radically change the treatment of very serious or chronic diseases with no therapeutic alternatives. To date, approximately 20 advanced therapies have been approved by the EMA, and many more are currently under investigation[20].

In this regard, two recently published reviews by Jorgensen et al. (2020)[21] and Ronco et al. (2021)[22] showed how the reimbursement procedure for ATMPs is carried out in 5 European countries (Italy, France, United Kingdom, Germany, and Spain), finding that only chimeric antigen receptor T-cell (CAR-T) therapies Kymriah® and Yescarta® were reimbursed relatively homogeneously in all of them (Table 1). Thus, while in France and the UK reimbursement for these drugs, indicated for certain tumor types, is subject to additional data collection and conditional on future re-evaluations, in the other countries reimbursement (Germany) or tiered payments (Italy and Spain) are linked to the results obtained for each patient. The procurement of these therapies by state governments costs approximately 300,000 euros per successful patient. In addition, in France, a fixed supplement of 15,000 euros was added to the current Diagnosis-Related Group (DRG) system fee[21,22].

However, the reimbursement of ATMPs at the national level, like that of other drugs, appears to be highly heterogeneous throughout Europe, which can be explained by the healthcare organization of the different countries under study:

- In Italy and Spain, a very similar financing system for ATMPs is observed, based mostly on payment for results, as we mentioned before. In this way, in Italy, Holoclar® and Strimvelis® have been acquired for an amount of €95,000 and €594,000, respectively[21]; therapies that were not financed in Spain[22]. On the contrary, Alofisel® is funded in Spain, although with restrictions on the authorized indication[23]. In this case, a payment-by-results agreement was

TABLE 1. ATMPS FUNDING SCHEMES IN THE EU-5 (ITALY, UK, FRANCE, GERMANY AND SPAIN)

| COUNTRY | ITALY | | UNITED KINGDOM | | FRANCE | | GERMANY | | SPAIN | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ATMP | Type of RSA | Price, discount | Type of RSA | Price, discount | Type of RSA | Price, discount | Type of RSA | Price, discount | State | Type of RSA | Price, discount |
| Holoclar® | Payment by results | €95,000 | PAS | €88,993 (excluding confidential discount) | ASMR IV | Reimbursed according to DRG | NUB4 | Price DRG | Not funded by resolution | - | - |
| Imlygic® | - | - | PAS | €1,858/vial (excluding confidential discount) | - | - | NUB1 | €1,220.52 (after negotiation) | Not funded by resolution | - | - |
| Strimvelis® | Payment by results | €594,000 | - | €594,000 | - | - | - | -. | Not available | - | - |
| Spherox® | - | - | - | €11,124 (excluding confidential discount) | - | Reimbursed according to DRG | - | - | Not available | - | - |
| Alofisel® | - | - | - | €60,083 | ASMR IV | €54,000 | NUB1 | €60,000 | Funded | Monitoring and payment by results | €60,000 |
| Kymriah® | Payment by results | €320,000 (discount for LBDCG) | CDF (MAA, CAA) | €313,766 ((excluding confidential discount) | ASMR IV for LBDCG; ASMR III for LLA | €297,666 + €15,000 above DRG | NUB1 | €320,000 | Funded with restrictions for both indications (LBDCG and ALL) | Monitoring and payment by results | €320,000 |
| Yescarta® | Payment by results | €327,000, discount | CDF (MAA, CAA) | Confidential price + discount | ASMR III | €327,000 + €15,00 over DRG | NUB1 | €327,000 | Funded with restrictions for both indications (LBDCG and LBPM) | Monitoring and payment by results | €327,000 |
| Luxturna® | - | - | - | €682,673 | ASMR III | - | NUB1 | €345,000 | Funded | Monitoring and expenditure ceiling | - |

Abbreviations: **ASMR**: Amélioration du Service Médical Rendu; **ATMP**: Advanced Therapy Medicinal Product; **CAA**: Commercial Access Agreements, **CDF**: Cancer Drug Funds; **DRG**: Diagnosis Related Group; **LBDCG**: Diffuse Large B-cell Lymphoma; **LLA**: Acute Lymphoblastic Leukemia; **MAA**: Managed Access Agreements; **NUB**: Neue Untersuchungs-und Behandlungsmethoden, extra budgetary reimbursement; **PAS**: Patient Access Scheme; **RSA**: Risk sharing agreement

Source: *own elaboration based on* Jørgensen (2020)[21] *y Ronco* (2021)[22]

reached for a total of €60,000[22], and an annual review of sales and fixed prices was agreed upon to ensure that they are within legally established parameters and, if not, to proceed with the corresponding price reduction[24].

- United Kingdom has a similar situation. There, ATMPs have been acquired through PAS, sometimes with confidential discounts.
- In the case of France, reimbursement of ATMPs has been carried out through the assignment of therapeutic benefit (SMR, which consists of 4 levels and 5 criteria) and added therapeutic value of the drug (ASMR, which is a 5-level system, where level I represents the highest added value). In this sense, reimbursement for Alofisel® was 10% cheaper than in Spain and therapies such as Holoclar® and Spherox® were fully reimbursed by the DRG[22].
- Finally, in Germany, an extrabudgetary reimbursement (NUB, Neue Untersuchungs-und Behandlungsmethoden, new examination and treatment method) has been requested for all ATMPs with financing agreement. This is possible when a drug is used in the hospital

setting and its price is not fully covered by a DRG fee.

This example shows that there is no single approach to reimbursement and access to ATMPs in the European Union, which undoubtedly poses a huge challenge. However, the available evidence so far allows us to conclude that[25]:

- ATMPs can be profitable at the high prices set by manufacturers.
- The economic evaluation framework adopted by many payers undervalues these therapies, which negatively impacts patient access.
- ATMPs can be affordable and may not require deferred payments.
- Outcomes-based agreements can be challenging to implement in real-world practice.
- The profitability of ATMPs depends on the type of agreement and payment approach.
- Greater collaboration between different countries would allow for better management of reimbursement and access to ATMPs

## EXAMPLES OF INNOVATIVE FINANCING MODELS FOR RD IN SPAIN

In Spain, concern for the sustainability of the healthcare system has also promoted the adoption of different schemes for the ODs financing, although their confidential nature prevents a detailed analysis of them, so we have to limit ourselves to the information collected in the available literature and that disclosed by health authorities, media, and other stakeholders.

At the national level, the Spanish Ministry of Health has echoed on several occasions the importance of applying payment for results agreements to reduce uncertainty in clinical and budgetary impact, measuring results in clinical practice and evaluating compliance in each patient so that the National Health System only pays the full price of the medicine in those patients where the treatment achieves the expected therapeutic goal[26,27].

**The Spanish Ministry of Health has recognized the importance of implementing payment by results agreements to reduce uncertainty regarding the clinical and budgetary impact**

In 2019, VALTERMED was created, a shared information system within the National Health System that allows measuring the health outcomes achieved by publicly financed latest-generation medicines, in order to share real information and improve the efficiency of the system. The medicines included in VALTERMED are high-cost drugs that are generally subject to payment for results agreements. The first one was CAR-T tisagenlecleucel (with OD designation), which was the subject to an innovative financing agreement[28] of 327,000, with a first payment of 50% once the drug infusion was completed and a second payment at 18 months of treatment based on the response obtained in terms of overall survival[22,29].

Currently, 79% of the drugs included in VALTERMED (11 out of 14 in total) are ODs, for which a pharmacoclinical protocol is developed and monitoring is carried out through the system. Eight of them are financed through a health outcomes-based risk-sharing agreement, and three through a financial outcomes-based RSA (supply at lower cost, maximum cost per patient, cost ceiling)[28] (Table 2).

Regional health authorities have also been proactive in making innovative financing agreements for ODs. Catalonia has been one of the most active autonomous communities in this regard. In fact, during the period 2016-2019, the Catalan Health Service (CatSalut) launched 3 RSAs (still in force) involving ODs, which represents 20% (3/15) of all agreements signed during that period[30]. These drugs would be intended to meet therapeutic needs in the respiratory, gastroenterology and nephrology fields (the disease for which they would be indicated has not been disclosed in order to avoid the identification of the drug) and were financed, at the regional level, through financial outcomes-based agreements (specifically, price-volume agreements and annual budget limits)[30], although it has not been possible to obtain more information about them.

However, in Spain, most of the RSA agreements are signed in the hospital setting. In this regard, a survey of 80 members of the Spanish Society of Hospital Pharmacy (SEFH)

TABLE 2. LIST OF ODS INCLUDED IN VALTERMED AND FINANCED IN SPAIN THROUGH RISK-SHARING AGREEMENTS

| ACTIVE INGREDIENT | MEDICINE® | PRESENTATION | ABBREVIATED INDICATION | SPECIAL FINANCING CONDITIONS |
|---|---|---|---|---|
| **Tisagenlecleucel** | Kymriah | 1,2x10$^{6}$-6,0x10$^{8}$ cells dispersion for perfusion | Refractory or relapsed B-cell acute lymphoblastic leukemia (ALL) | - Risk groups<br>- Pharmacoclinical protocol<br>- Patient registration: risk sharing/payment by results<br>- Follow-up<br>- Provision to certain patients free of charge |
| **Axicabtagén ciloleucel** | Yescarta | 0,4-2x10$^{8}$ cells dispersion for infusion | Relapsed or refractory diffuse large B-cell lymphoma (DLBCL) | |
| **Inotuzumab onogamicina** | Besponsa | 1 mg powder for concentrate for solution for infusion | Recurrent or refractory CD22-positive B-lymphocyte precursor acute lymphoblastic leukaemia (ALL) | - Pharmacoclinical protocol<br>- Patient registration: risk sharing/payment by results<br>- Follow-up<br>- Provision to certain patients free of charge |
| **Darvadstrocel** | Alofisel | 5 million cells/ml suspension for injection | Complex perianal fistulas in patients with Crohn's disease | - Pharmacoclinical protocol<br>- Risk sharing/payment by results<br>- Follow-up |
| **Tezacaftor/ivacaftor** | Symkevi | 100/150 mg film-coated tablets | Cystic fibrosis | - Pharmacoclinical protocol<br>- Follow-up<br>- Lower cost supply |
| **Burosumab** | Crysvita | 10, 20 and 30 mg solution for injection | X-linked hypophosphatemic rickets | - Maximum cost per patient<br>- Pharmacoclinical protocol<br>- Risk sharing/payment by results<br>- Follow-up |
| **Voretigén neparvovec** | Luxturna | 5x10$^{12}$ vector genomes /ml concentrate and solvent for solution for injection | Retinal dystrophy associated with RPE65 mutation | · Protocolo<br>- Follow-up<br>- Expenditure ceiling |
| **Vestronidasa alfa** | Mepsevii | 2 mg/ml concentrado para solución para perfusión | Manifestaciones no neurológicas de la mucopolisacaridosis VII (síndrome de Sly) | · Coste máximo por paciente<br>· Protocolo<br>· Seguimiento |
| **Polatuzumab vedotina** | Polivy | 30/140 mg powder for concentrate for solution for infusion | Relapsed or refractory LBDCG and in combination with bendamustine and rituximab | - Faramacoclinic protocol<br>- Risk sharing/payment by results<br>- Follow-up |
| **Onasemnogén abeparvovec** | Zolgensma | 2x10$^{13}$ vector genomes /ml solution for infusion | Spinal muscular atrophy | - Price/volume agreement<br>- pharmacoclinical protocol<br>- Risk sharing/payment by results<br>- Follow-up |
| **Volanesorsén** | Waylivra | 250 mg solution for injection in prefilled syringe | Familial chylomicronemia syndrome | - Maximum cost per patient<br>- Pharmacoclinical protocol<br>- Risk sharing/payment by results |

Source: *own elaboration based on VALTERMED*[28]

showed that the level of implementation of RSA in Spanish hospitals is high, as more than 90% declare that they are currently linked to this type of contract with the pharmaceutical industry and express their intention to renew or sign new ones[31]. Moreover, more than 60% of respondents prioritize innovative models based on payment for efficacy/efficiency in the case of agreements for rare diseases or orphan drugs[31].

Specifically, Edo-Solsona et al. (2020)[32] recently shared the first experience of pay-for-performance in a Spanish reference hospital (La Fe Hospital in Valencia) involving ODs for congenital metabolic diseases through a risk-sharing program for enzyme replacement therapies (ERT) in lysosomal storage diseases (LSD)[32] that result in physical deterioration, decreased functional capacity, and potentially death33. In this program, 8 patients (3 women and 5 men) with different LSDs were included: 4 patients with Hurler disease (mucopolysaccharidosis) who were treated with laronidase, 2 patients with Pompe disease (glycogenosis) who were given alglucosidase, and 2 patients with Gaucher disease (sphingolipidosis) who were treated with imiglucerase[32].

When establishing the agreement, the variables and criteria for response to treatment were defined for each ERT, selected according to the experience of the practitioners and the available evidence (Table 3)[32]. Thus, for example, the effectiveness of laronidase was evaluated through the reduction in the excretion of glycosaminoglycans in urine, the improvement of pulmonary, hepatic and splenic capacities, and depending on how much the natural progression of the disease decreased, at one and two years of treatment[32].

It should be noted that, so far, the authors indicate that the economic impact of implementing the ERT program on patients has been very limited, as the treatments have shown full effectiveness after two or three years of follow-up, and in this case, the hospital proceeded to full payment for all therapies administered[32]. This example, the only one published in detail so far for a rare disease in Spain, highlights the need to increase the evaluation and transparency of agreements made.

**To maximize the potential advantages of these models for the future, the objectives of the agreement must be clearly defined, detailing the duties and obligations of the parties involved**

## CONCLUSIONS AND RECOMMENDATIONS FOR MAXIMIZING BENEFITS

Financing agreements for pharmaceutical innovations have become a common practice in healthcare systems when the price of the drug is high and there is uncertainty about its clinical and/or financial outcomes, which applies to a large portion of ODs. These agreements allow for risk-sharing and accelerate patient access to treatments, although their implementation also entails certain costs and administrative burden that can limit their use.

In any case, the decision to introduce an innovative financing model should take into account various aspects, such as the level of risk assumed, who bears it, what long-term effects it may entail, how the degree of achievement of results can be measured and quantified, who will analyze them, and who will manage them.

On the other hand, to maximize the potential benefits of these models for the future, it would be important to consider the following considerations. First, the objectives of the agreement must be clearly defined, detailing the duties and obligations of the parties involved. In this regard, it is recommended to jointly develop the agreement between the funder and the pharmaceutical company, including a deliberative process on how decisions will be linked to the results obtained. Second, it is imperative to orient these models towards the patient, also defining what is meant by therapeutic success and which (intermediate and final) measurement variables would be most appropriate. In turn, the process should be simplified, managing the models correctly to avoid a high administrative burden. Third, it is recommended to analyze their long-term impact, creating records and monitoring systems for the results that allow real-time tracking. Finally, for these models to be successful, it is necessary to provide the healthcare system with adequate material and human resources for their proper management, as well as to raise awareness about the importance of having an evaluative culture of innovation.

TABLE 3. EFFICACY AND RESPONSE CRITERIA IN THE RISH-SHARING PROGRAM FOR ENZYME REPLACEMENT THERAPIES FOR LYSOSOMAL STORAGE DISEASES

| | |
|---|---|
| **Hurler's disease**<br>Laronidase treatment (n=4) | |
| First year of treatment | |
| **Efficacy criteria** | **Primary:**<br>• Decreased urinary excretion of GAGs<br>**Secundary:**<br>• Improvement of respiratory tests (polysomnography and CVF)<br>• Age-related increase in liver and splenic volume<br>• Interruption of the natural progression of the disease |
| **Types of response** | • **Total:** GAG excretion >40%.<br>• **Moderate:** GAG excretion between 25-40%.<br>• **Mild:** GAG excretion <25%. |
| Second year of treatment | |
| **Efficacy criteria** | • Stabilisation or increase <5% of urinary GAGs<br>• Improvement or non-progression in respiratory tests<br>• Increased liver and splenic volume<br>• Interruption of the natural progression of the disease |
| **Types of response** | • **Total:** the patient meets all 4 criteria above<br>• **Moderate:** the patient does not meet any of the above criteria |
| **Pompe disease**<br>Alglucerase treatment (n=2) | |
| **Efficacy criteria** | • Measurement of muscle strength<br>• 6-minute walk test<br>• Forced vita capacity in seated and decubitus position |
| **Types of response** | • **Total:** Annual impairment <10%<br>• **Moderate:** Annual deterioration between 10-20% on some criteria<br>• **Mild:** Annual deterioration between 10-20%<br>• **No responsive:** annual deterioration >20% |
| **Gaucher disease**<br>Imiglucerase treatment (n=2) | |
| Adult patient | |
| Second year of treatment | |
| **Efficacy criteria** | • Normalization of plasma haemoglobin levels<br>• Normalization of plasma platelet levels<br>• Normalization of liver and splenic volume<br>• Reduction or remission of bone pain<br>• Maintenance of normal bone mineral density<br>• Absence of progression of the bone lesion present |
| **Types of response** | • **Complete:** the patient meets ≥4 of the above criteria<br>• **Moderate:** the patient meets 3 of the above criteria<br>• **No responsive:** patient meets ≤2 criteria above |
| Paediatric patient | |
| First and second year of treatment | |
| **Efficacy criteria** | **Primary:**<br>• Increase in plasma haemoglobin levels to normal for age<br>• Increase in plasma platelet levels to normal for age<br>• Avoiding splenectomy (removal of the spleen)<br>• Reduction of hepatosplenomegaly to avoid disease symptomatology<br>**Secundary:**<br>• Adequate growth following its growth curve<br>• Absence of pain or osteonecrosis<br>• Reduction of chitotriosidase enzyme and/or cytokine CCL18/PARC levels by 10%. |
| **Types of response** | • **Total:** patient meets 3 of the above primary criteria<br>• **Moderate:** the patient meets 2 of the primary criteria and 2 of the secondary criteria above<br>• **Mild:** the patient meets 1 of the primary criteria and ≤3 of the secondary criteria above |

Abbreviations: **CVF:** forced vital capacity; **GAG:** glycosaminoglycans

Source: *Edo-Solsona (2020)*[32]

1. Abellán JM, Garrido S, Martínez JE, Sánchez FI. Evidencia de los acuerdos de riesgo compartido como fórmula de cobertura de nuevas tecnologías sanitarias. Grupo de Investigación en Economía de la salud y evaluación económica. Departamento de Economía Aplicada. Universidad de Murcia [Internet]. 2010. Available from: *https://sms.carm.es/somosmas/documents/63024/0/ACUERDOS+RIESGO+COMPARTIDO.pdf/89dcfc0f-2e3e-4f27-8b79-f80a688a74ae*

2. Puig-Junoy J, Meneu R. Aplicación de los contratos de riesgo compartido a la financiación de nuevos medicamentos. Ges Clin Sanit. 2005;7:88–94.

3. Espín J, Oliva J, Rodríguez-Barrios JM. Esquemas innovadores de mejora del acceso al mercado de nuevas tecnologías: los acuerdos de riesgo compartido. Gac Sanit. 2010;24(6):491–7.

4. Garrison LP, Towse A, Briggs A, de Pouvourville G, Grueger J, Mohr PE, et al. Performance-based risk-sharing arrangements-good practices for design, implementation, and evaluation: report of the ISPOR good practices for performance-based risk-sharing arrangements task force. Value Health J Int Soc Pharmacoeconomics Outcomes Res. 2013;16(5):703–19.

5. Carlson JJ, Sullivan SD, Garrison LP, Neumann PJ, Veenstra DL. Linking payment to health outcomes: a taxonomy and examination of performance-based reimbursement schemes between healthcare payers and manufacturers. Health Policy Amst Neth. 2010;96(3):179–90.

6. Richter T, Nestler-Parr S, Babela R, Khan ZM, Tesoro T, Molsen E, et al. Rare Disease Terminology and Definitions-A Systematic Global Review: Report of the ISPOR Rare Disease Special Interest Group. Value Health J Int Soc Pharmacoeconomics Outcomes Res. 2015;18(6):906–14.

7. Iskrov G, Stefanov R. Post-marketing access to orphan drugs: a critical analysis of health technology assessment and reimbursement decision-making considerations. Orphan Drugs Res Rev. 2014;1.

8. Villa F, Di Filippo A, Pierantozzi A, Genazzani A, Addis A, Trifirò G, et al. Orphan Drug Prices and Epidemiology of Rare Diseases: A Cross-Sectional Study in Italy in the Years 2014-2019. Front Med. 2022;9:820757.

9. Nuijten M, Van Wilder P. The impact of early phase price agreements on prices of orphan drugs. BMC Health Serv Res. 2021 Mar 12;21:222.

10. Brenna E, Polistena B, Spandonaro F. The implementation of health technology assessment principles in public decisions concerning orphan drugs. Eur J Clin Pharmacol. 2020;76(6):755–64.

11. Morel T, Arickx F, Befrits G, Siviero P, van der Meijden C, Xoxi E, et al. Reconciling uncertainty of costs and outcomes with the need for access to orphan medicinal products: a comparative study of managed entry agreements across seven European countries. Orphanet J Rare Dis. 2013;8:198.

12. Fundación Gaspar Negrín. Libro Blanco de las enfermedades raras en España. 2018.

13. National Institute for Health and Care Excellence. Patient Access Schemes Liaison Unit | What we do | About [Internet]. NICE. NICE; [cited 2022 Aug 4]. Available from: *https://www.nice.org.uk/about/what-we-do/patient-access-schemes-liaison-unit*

14. Spinal Muscular Atrophy UK. Managed Access Agreement FAQs - [Internet]. [cited 2022 Aug 4]. Available from: *https://smauk.org.uk/managed-access-agreement-faqs*

15. Blonda A, Barcina Lacosta T, Toumi M, Simoens S. Assessing the Value of Nusinersen for Spinal Muscular Atrophy: A Comparative Analysis of Reimbursement Submission and Appraisal in European Countries. Front Pharmacol. 2022 Jan 21;12:750742.

16. National Heatlh Service in England. Patient Access Scheme(s) Project [Internet]. [cited 2022 Aug 4]. Available from: *https://www.lpp.nhs.uk/categories/medicines-optimisation-pharmacy-procurement/medicines-procurement/patient-access-scheme(s)-project/*

17. Xoxi E, Facey KM, Cicchetti A. The Evolution of AIFA Registries to Support Managed Entry Agreements for

Orphan Medicinal Products in Italy. Front Pharmacol. 2021;12:699466.

18. Adamski J, Godman B, Ofierska-Sujkowska G, Osinska B, Herholz H, Wendykowska K, et al. Risk sharing arrangements for pharmaceuticals: potential considerations and recommendations for European payers. BMC Health Serv Res. 2010;10:153.

19. Orchard Therapeutics Reports First Quarter 2022 Financial Results and Highlights Recent Commercial Progress | Orchard Therapeutics [Internet]. [cited 2022 Aug 4]. Available from: https://ir.orchard-tx.com/news-releases/news-release-details/orchard-therapeutics-reports-first-quarter-2022-financial/

20. EMA. Advanced therapy medicinal products: Overview [Internet]. European Medicines Agency. 2021 [cited 2022 Apr 4]. Available from: https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview

21. Jørgensen J, Hanna E, Kefalas P. Outcomes-based reimbursement for gene therapies in practice: the experience of recently launched CAR-T cell therapies in major European countries. J Mark Access Health Policy. 2020;8(1):1715536.

22. Ronco V, Dilecce M, Lanati E, Canonico PL, Jommi C. Price and reimbursement of advanced therapeutic medicinal products in Europe: are assessment and appraisal diverging from expert recommendations? J Pharm Policy Pract. 2021;14(1):30.

23. Ministerio de Sanidad. Buscador situación financiación medicamentos (BIFIMED) [Internet]. 2022 [cited 2022 Aug 8]. Available from: https://www.sanidad.gob.es/profesionales/medicamentos.do

24. Ministerio de Sanidad. Acuerdos de la Comisión Interministerial de Precios de Medicamentos (CIPM).

25. Simoens S, De Groote K, Boersma C. Critical Reflections on Reimbursement and Access of Advanced Therapies. Front Pharmacol. 2022;13:771966.

26. Ministerio de Sanidad. Nota de Prensa. Carcedo: Valtermed permitirá generar información para la toma de decisiones sobre la mejor opción terapéutica para los pacientes [Internet]. 2019 [cited 2022 Aug 23]. Available from: https://www.sanidad.gob.es/gabinete/notasPrensa.do?id=4697

27. Redacción Médica. El nuevo pago de fármacos por resultados es "igualitario e individualizado" [Internet]. Redacción Médica. [cited 2022 Aug 23]. Available from: https://www.redaccionmedica.com/secciones/industria/el-nuevo-pago-de-farmacos-por-resultados-es-igualitario-e-individualizado--1677

28. Ministerio de Sanidad. Sistema de Información para determinar el Valor Terapéutico en la Práctica Clínica Real de los Medicamentos de Alto Impacto Sanitario y Económico en el SNS (VALTERMED) [Internet]. 2022 [cited 2022 Aug 4]. Available from: https://www.sanidad.gob.es/profesionales/farmacia/valtermed/home.htm

29. Consejo de Transparencia y Protección de Datos de Andalucía. Resolución 340/2021, de 27 de mayo [Internet]. [cited 2022 Aug 23]. Available from: https://www.ctpdandalucia.es/sites/default/files/resoluciones/res-340-2021.pdf

30. Guarga L, Gasol M, Reyes A, Roig M, Alonso E, Clopés A, et al. Implementing Risk-Sharing Arrangements for Innovative Medicines: The Experience in Catalonia (Spain). Value Health J Int Soc Pharmacoeconomics Outcomes Res. 2022;25(5):803–9.

31. Lorente R, Antonanzas F, Rodriguez-Ibeas R. Implementation of risk-sharing contracts as perceived by Spanish hospital pharmacists. Health Econ Rev. 2019;9(1):25.

32. Edo-Solsona MD, Vitoria-Miñana I, Poveda-Andrés JL. Implementation and results of a risk-sharing scheme for enzyme replacement therapy in lysosomal storage diseases. Farm Hosp Organo Of Expresion Cient Soc Espanola Farm Hosp. 2020;44(1):10–5.

33. Ratko TA, Marbella A, Godfrey S, Aronson N, Ratko TA, Marbella A, et al. Terapias de reemplazo de enzimas para enfermedades de almacenamiento lisosomal. Agencia para la Investigación y la Calidad de la Atención Médica (EE. UU.); 2013.

# OPTIMIZATION ELEMENTS IN RARE DISEASES: EUROPEAN FUNDS

CARLOS DÉVORA, IRENE FERNÁNDEZ, FERNANDO ABDALLA, NÉBOA ZOZAYA

*Department of Health Economics & Market Access, and Health Affairs & Policy Research, Vivactis Weber*

There are still enormous challenges in terms of unmet medical needs for people living with rare diseases (RDs). Despite each of these diseases being individually rare, they altogether affect more than 36 million people in the European Union (EU)[1] and approximately 3 million people in Spain[2].

The main challenge in optimizing the management of RDs is to understand the mechanisms of the more than 6,000 known RDs to date[3] and to ensure that research and innovation effectively translate into new diagnostics and effective treatments. Since the patients population affected by each pathology are small and dispersed, there is a scarcity and fragmentation of knowledge and expertise, so the potential return on R&D of drugs to treat these diseases is limited[4]. For all these reasons, the field of RDs is an area where international collaboration is a prerequisite for progress[1].

In recent years, there have been advances in various strategic areas to improve the quality of life of people living with a RD through the approval of regulatory frameworks, prioritization in healthcare policy aspects, the creation of support networks, or the increase in research activity, among others[5]. At the European level, research in the field of RDs has been widely supported through Research and Innovation Framework

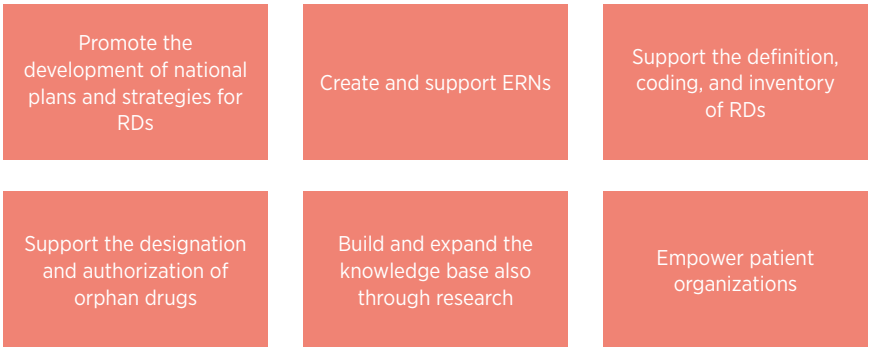
Programs by financing projects that promote basic and translational research, the development of new therapies, diagnostic tools, technological aspects, and the creation of research networks or infrastructures for better data integration[4,6].

The objective of this article is to review how European funds have promoted the optimization of the management of patients with RDs. To do this, we will classify the main types of European funds (historical and current situation) focused on the field of RDs. We will also provide examples of specific projects funded by European funds with Spanish participation. Finally, we will suggest some proposals so that European funds and investment in research can benefit patients with rare diseases in a more efficient manner.

## HISTORICAL CONTEXT

The strategic objective for optimizing the management of RDs in the EU is to improve patient access to diagnosis, information, and healthcare[1]. To achieve this, the European response must combine a series of key elements that ultimately help to pool the scarce resources distributed throughout the EU, allowing patients and professionals to share knowledge and information (Figure 1).

FIGURE 1. KEY ELEMENTS OF THE EUROPEAN RESPONSE TO OPTIMIZE THE TACKLING OF RDs



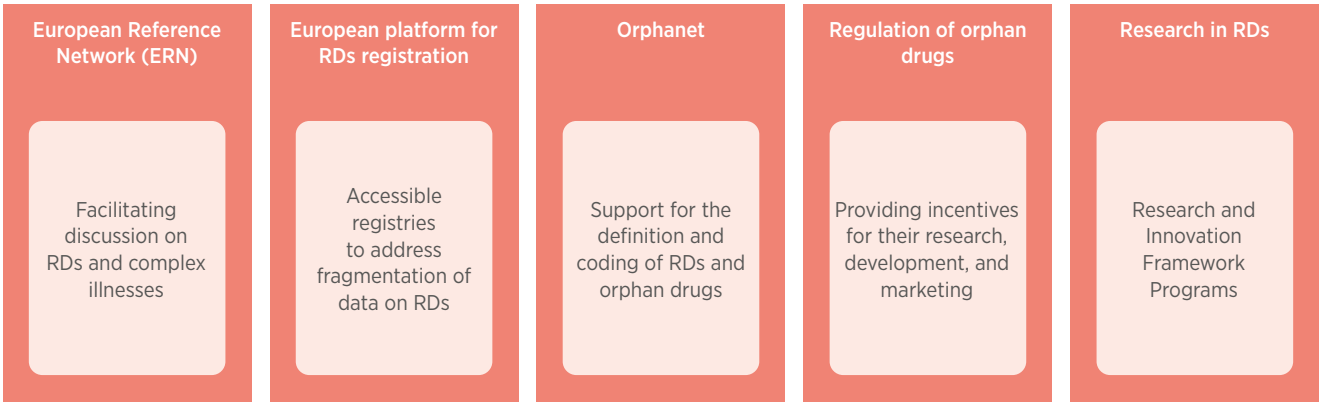

**ERN**: European Reference Networks; **RDs**: Rare Diseases

Source: *own elaboration based on European Commission (2022)*[1]

In line with this, the European Commission has focused on developing cooperation, coordination and regulation at EU level, including through the creation of European Reference Networks (ERNs), legislation on orphan medicinal products (OMPs) and funding for research and development projects. In addition, to improve the recognition and visibility of ODs, a registration platform and the Orphanet network have been set up to provide high quality information on ODs and to ensure equal access to knowledge for all stakeholders[1] (Figure 2).

Since 1984, the EU's research and technological development activi-

FIGURE 2. MAIN ACTIONS OF THE EUROPEAN COMMISSION FOR TACKLING RDs




**RDs**: Rare Diseases

Source: *own elaboration based on European Commission (2022)*[1]

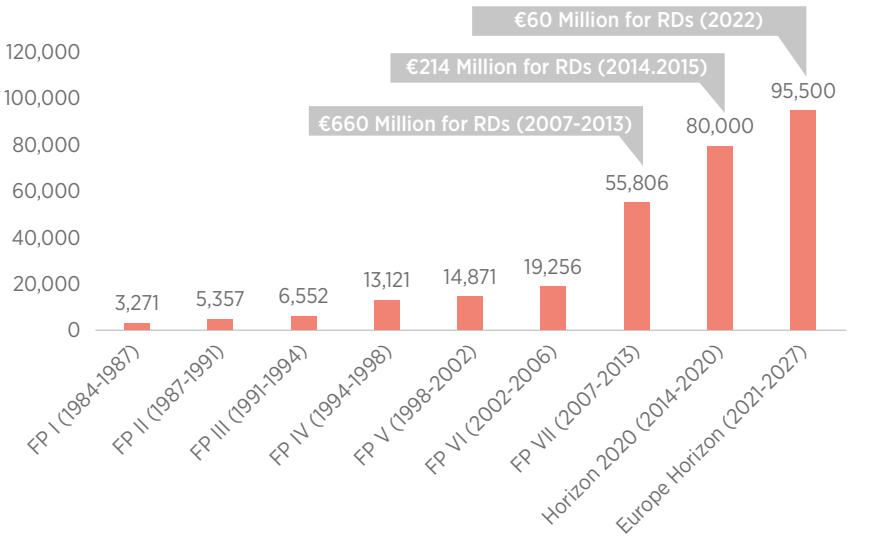
ties have been defined and implemented through a series of multi-year Framework Programs (FPs) that are proposed by the European Commission and adopted by the Council and the European Parliament following a co-decision procedure[7]. These programs have positioned themselves as the EU's main financial tools for supporting research and development activities, covering almost all scientific disciplines thanks to a budget amount to be distributed over the years of the period, to which private and state public investment is added.

Since the 7th Framework Programme (2007-2013), projects of relevance for rare diseases research have been included and have continued to receive support within Horizon 2020 (2014-2020), which promoted a strategy with the aim of developing new diagnostic methods and treatments for rare diseases. Efforts in this area will continue with Horizon Europe (2021-2027), which also includes greater patient involvement in decision-making[4]. The substantial increase in the budget allocated to the Framework Programmes over the years reflects the high priority of research in Europe[8] (Figure 3).

The European funds for research in RDs from 2007 to 2020 (7th FP and Horizon 2020) were dedicated to more than 440 projects in multinational research consortia[12].

In a report published by the European Commission in 2017, the results of a selection of 164 projects were analyzed based on their relevance to research on RDs, of which 120 were funded under the Health theme of the 7th Framework Programme, and the remainder under the Health, Demographic Change and Wellbeing challenge of Horizon 2020. Beyond the projects included in this report, there are other potential projects that contribute to the objectives of RDs in other thematic areas of the 7th Framework Programme and Horizon 2020, among which stand out:

FIGURE 3. BUDGET OF THE RESEARCH FRAMEWORK PROGRAMMES (IN MILLIONS OF EUROS)




**FP**: Framework Programme; **RDs**: Rare Diseases

Note: *FPI-FPVII budgets correspond to EUR 2013*

Source: *own elaboration, based on European Commission (2013)[9] and European Commission (2022)[10,11]*

- Future and Emerging Technologies (FET-Open) calls to support early-stage research and innovation in emerging technologies[13].
- Marie Sklodowska-Curie Actions (MSCA) to strengthen, quantitatively and qualitatively, the human potential in research and technology[14].
- European research infrastructure programs to provide resources and services to research communities[15].
- Grants from the European Innovation Council (EIC) to identify, develop, and scale up breakthrough technologies and innovations[16].
- Grants from the European Research Council (ERC) to promote frontier research based on scientific excellence through competitive funding[17].

The EU's funding strategy for research on RDs focuses on understanding the underlying causes of these diseases, as well as on diagnosis, prevention, and treatment, thus combining advances in scientific knowledge in this field with benefits for patients with RDs[4]. In addition, projects are funded to coordinate and support the research area, with specific initiatives that provide a solid framework for improving cooperation in the area of RDs[12] (Figure 4).

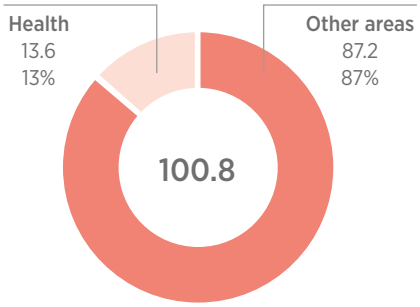
FIGURE 4. YEAR OF LAUNCHING AND OBJECTIVES OF THE PROGRAMS AND COORDINATION CONSORTIA

| IRDiRC | EJP RD | ERICA |
|---|---|---|
| • 2011<br>• To accelerate medical advances for people affected by rare diseases | • 2019<br>• To create a global and sustainable ecosystem that allows for a virtuous circle between research, medical care, and innovation | • 2021<br>• To coordinate clinical research activities of ERNs |

**EJP RD**: European Joint Programme on Rare Diseases; **ERICA**: European Rare disease research Coordination and support Action Consortium; **IRDiRC**: International Rare Diseases Research Consortium; **ERN**: European Reference Networks; **RDs**: Rare Diseases

Source: *own elaboration based European Commission (2022)*[12]

FIGURE 5. BUDGETS 2021-2027 OF HORIZON EUROPE AND EU4HEALTH (IN BILLIONS OF EUROS)




Source: *own elaboration based on European Commission (2022)*[20,21]

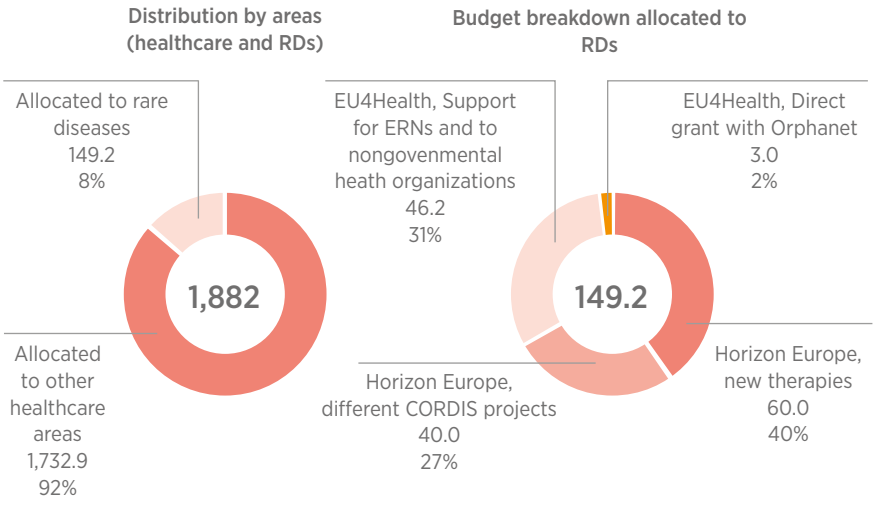
## EUROPEAN FUNDS 2021-2027

Horizon Europe is the current EU Research and Innovation (R&I) programme with a budget of over €95.5 billion for the period of 2021-2027, the highest of any previous designated budgets. It focuses on areas of special urgency and need at the European level, where isolated actions by the Member States are insufficient or less effective than transnational collaboration. The programme consists of a structure based on three pillars called "Excellent Science", "Global Challenges and European Industrial Competitiveness" and "Innovative Europe", which are supported by a cross-cutting axis focused on expanding participation and strengthening the European Research Area (ERA)[18].

Beyond the contribution of Horizon Europe, after the COVID-19 pandemic, the EUproHealth budget program was launched at the European level as a response to strengthen crisis preparedness and contribute to long-term health challenges by creating stronger, more resilient, and accessible healthcare systems. The EUproHealth (2021-2027) has a budget of 5.3 billion euros[19], which brings the total budget for these two programs for the EU in the period 2021-2027 to over 100 billion euros, of which 13% has been allocated to the health area (i.e. about 13.6 billion euros) (Figure 5).

Regarding health, the annual budget of these two programs for 2022 amounts to 1.882 billion euros, of which 8% has been allocated to projects that directly or indirectly support research and innovation in RDs. More than half of the European investment dedicated to RDs throughout 2022 comes from Horizon Europe and is focused on the development of new therapies and various research projects; the remaining investment from EU4Health for RDs has mainly consisted of supporting the European Reference Networks and non-governmental health organizations (Figure 6).

FIGURE 6. BUDGETS 2022 OF HORIZON EUROPE AND EU4HEALTH (IN MILLION EUROS)




**RDs**: Rare Diseases, **ERN**: European Reference Networks, **CORDIS**: Community Research and Development Information Service

Source: *own elaboration based on European Commission (2022)*[20,21]

TABLE 1. PROJECTS AND PROGRAMS FUNDED BY THE HORIZON EUROPE PROGRAM (2021-2027) AND EU4HEALTH (2021-2027) INCLUDED IN THE 2022 ANNUAL BUDGET AND SPECIFICALLY AIMED AT RARE DISEASES

| Project/program | Objective | Amount (€, millions) | Duration | Coordination | Spanish participation |
|---|---|---|---|---|---|
| HORIZON EUROPE | | | | | |
| HORIZON-HLTH-2022-DISEASE-06-04-two-stage | Developing therapies for RDs without an approved therapeutic option | 60.0 | N.A. | N.A. | N.A. |
| GetRAdi | Improving the transfer and efficiency of genome editing tools and the safety of gene therapy | 2.8 | 09/2022-08/2026 | Denmark | No |
| NeuroDiDro | Identify the neural and developmental basis of autophagy-associated neurodegeneration and discover the molecular responses of BPAN disease | 0.2 | 10/2022-09/2024 | France | No |
| Chrom_rare | Revealing the molecular basis of chromatinopathies to delineate innovative therapeutic solutions | 2.4 | 01/2023-12/2026 | Italy | Yes (through CSIC) |
| MRDAML | Deciphering the mechanical basis of MRD and treatment resistance in acute myeloid leukemia | 0.2 | 09/2023-08/2025 | Germany | No |
| FeverTime | Obtain key results on the evolution and spread of familial Mediterranean fever | 0.2 | 01/2023-12/2024 | Ireland | No |
| (TREM2MICROENGINES) | To demonstrate the role of TREM2 microglia in the treatment of dementias (Alzheimer's disease and Nasu-Hakola disease) | 0.2 | 07/2022-12/2023 | Italy | No |
| SBS-microbe | To identify microbial and cellular biomarkers of short bowel syndrome in a combined in vitro-in vivo study | 0.2 | 01/2023-12/2024 | Belgium | No |
| miRSodium | To analyse miRNA regulation of sodium channel isoform transition in development and its implications in Dravet syndrome | 0.2 | 09/2022-08/2024 | Ireland | No |
| EU4Health | | | | | |
| DP-g-22-26.01 | Ensure the participation of healthcare NGOs in the activities necessary to implement one or more specific objectives of the EU4Health program | 9.0 | N.A. | N.A. | N.A. |
| HS-g-22-16.01 | Support the Coordinating Centers of the 24 ERNs for the coordination and management of their operational activities (including the integration of more than 600 new units and affiliated partners) | 26.0 | N.A. | N.A. | N.A. |
| HS-g-22-16.02 | Supporting the integration of ERNs into Member States' national health systems | 11.2 | N.A. | N.A. | N.A. |
| HS-g-22-16.03 | Integrate the Orphanet nomenclature and orphan codes as the main coding system for RDs in the IT systems of ERNs and healthcare providers, and the continuous maintenance, updating and improvement of the system based on scientific analysis of the state-of-the-art knowledge in the field of EERRs. Furthermore, ensure harmonisation with other coding systems (e.g. SNOMED) | 3.0 | N.A. | N.A. | N.A. |
| Total | | 115.6 | | | |
| Subtotal Horizon Europe | | 66.4 | | | |
| Subtotal EU4Health | | 49.2 | | | |

Methodological note: *a search was conducted on the CORDIS database using the keyword "rare diseases". The filters "projects" and "programme: HORIZON" were applied. From the results obtained, a selection of specific projects for rare diseases was made*

Sources: *own elaboration based on European Commission (2022)*[20,21]

**BPAN**: beta-helix protein-associated neurodegeneration; **CSIC**: Centro Superior de Investigaciones Científicas; **RDs**: Rare diseases; **MRD**: minimal residual disease; **miRNA**: micro-deoxyribonucleic acid; **NGO**: Non-Governmental Organisation; **ERN**: European Reference Network; **SNOMED**: Systematised Nomenclature of Medicine

Within the 2022 budget allocated to Rare Diseases in Horizon Europe and EU4Health, we estimate that around €115.6 million[22] (77% of the total) correspond to projects specifically focused on rare disease research, while the remaining 33.4 million euros are allocated to more general projects that could also benefit rare diseases (Table 1).

Among the projects of Horizon Europe, the second phase of the HORIZON-HLTH-2022-DISEASE-06-04 call has allocated a total of 60 million in 2022 to contribute to the objectives of the International Rare Diseases Research Consortium (IRDiRC), which supports the development of around 1,000 innovative therapies for rare diseases by 2027, from small molecules to advanced therapy medicinal products, including drug repurposing and non-pharmacological interventions and/or their combinations[23].

**The strategic objective for optimization the tackling of RDs in the EU is to improve patients' access to diagnosis, information and healthcare**

The other projects under the Horizon Europe Program (totaling 6.4 million euros) aim to overcome the difficulties that hinder the widespread use of gene therapy (with the GetRAdi project and an allocation of 2.8 million euros) and to address research needs, mainly in the field of molecular biology, with initiatives focused on expanding the etiological knowledge of certain rare diseases[20]. An example of these is the Chrom_rare project, led by Italy and with the participation of Spain through the Spanish National Research Council (CSIC), which, with a budget of 2.4 million euros, will address the molecular basis of chromatinopathies with the aim of obtaining innovative therapeutic solutions[20].

On the other hand, the EU4Health program has allocated a total of 49.2 million in 2022 for different

TABLE 2. PROJECTS AND PROGRAMS FUNDED BY THE HORIZON EUROPE PROGRAM (2021-2027) AND EU4HEALTH (2021-2027) INCLUDED IN THE 2022 ANNUAL BUDGET AND FROM WHICH RARE DISEASES COULD BENEFIT

| Proyect | Objective | Amount, (€ million) | Coordination | Spanish participation |
|---|---|---|---|---|
| REMEDI4ALL | Build a sustainable European innovation platform to improve drug reutilization | 22.5 | The Netherlands | Yes (through TEAM-IT RESEARCH S.L., CHEMO-TARGETS S.L. and the Madrid Health Service) |
| NADIS NAD+ | Train scientists in the most advanced tools to study the relationship between NAD+ and metabolic health at different levels | 2.5 | The Netherlands | No |
| AAVolution | Studying next-generation AAV vectors for liver-targeted gene therapy | 4.0 | Italy | Yes (through FIMA) |
| DOSAGE2FUNC | Study gene expression dosage as a driver of cellular and physiological traits | 2.0 | Sweden | No |
| CASSIS | Consolidating a single-cell atlas of human soft tissue sarcoma ecosystems focused on immune evasion mechanisms | 0.2 | Germany | No |
| BioPIM | Create in-memory processing architectures and programming libraries for bioinformatics algorithms | 2.0 | Turkey | No |
| Rnable | Enabling greater accessibility to stem cell transplantation based on DNA and nanotechnology | 0.2 | Sweden | No |
| Total | | 33.4 | | |

Methodological note: *a search was carried out in the CORDIS database, using the term "rare diseases" as a keyword. The filters "projects" and "programme: HORIZON" were applied. Based on the results obtained, a selection of projects that could benefit rare diseases (apart from other common diseases) was made*

**AAV**: adenovirus-associated vectors; **DNA**: deoxyribonucleic acid; **FIMA**: Foundation for Applied Medical Research

Sources: *own elaboration based on European Commission (2022)*[20,21]

lines and areas of action in RDs. Through action line DP-g-22-26.01, with a budget of €9 million, the aim is to ensure the participation of healthcare NGOs in activities aimed at promoting health and preventing disease. The remaining 40.2 million is aimed at improving health systems by supporting the integration of European Reference Networks and the Orphanet disease coding tools, which are essential for improving the visibility of rare diseases in health information systems and for research[20].

In addition, among the projects funded by the Horizon Europe Program (2021-2027), we have made a selection of those that could benefit rare diseases (in addition to other more common diseases) (Table 2). Such projects, with a total budget of 33.4 million euros, would promote research in fields such as immunology, oncology, and proteomics, among others[20].

The project with the greatest economic impact is REMEDI4ALL, which with a budget of 22.5 million euros over the next 5 years, is focused on drug repurposing in Europe, a practice that is becoming increasingly important in medicine, especially in the area of RDs[24]. In this sense, the process of repurposing drugs for new indications, compared to the development of new medicinal products, is considered a useful method for shortening times to access innovative therapies, resulting in higher success rates against RDs[25].

## SPANISH FUNDS 2021-2023

In Spain, the Strategic Projects for Economic Recovery and Transformation (PERTE), divided into 11 areas of interest, also allocate a significant amount of the total budget to health, benefiting directly or indirectly RDs[26].

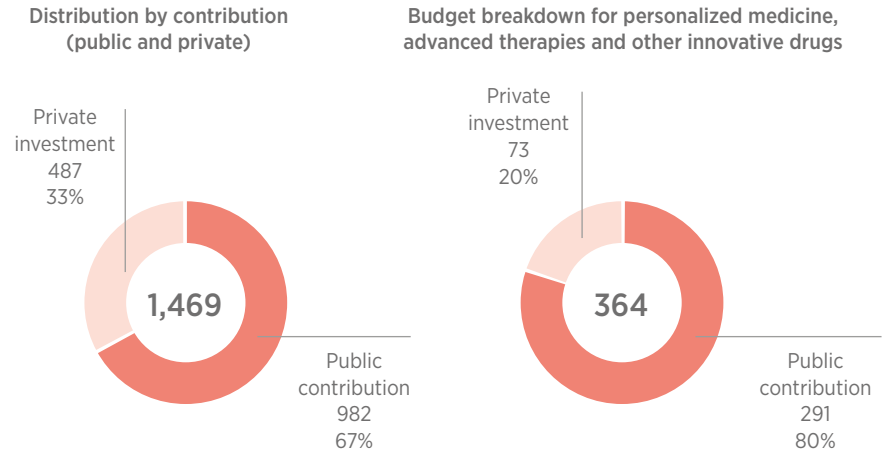
**The European Commission has focused on developing cooperation, coordination and regulation at the EU level, in order to improve recognition and visibility of RDs and enable patients and professionals to share knowledge and information**

Specifically, the PERTE for Vanguard Health, approved by the Council of Ministers on November 30, 2021, **has an initial investment of 1,469 billion euros in the period 2021-2023** (with a public sector contribution of 982 million euros and a private investment of 487 million euros), with the aim of improving population health through diagnostic, therapeutic, and preventive innovation in the Spanish National Health System[27].

Thus, the design and implementation of several health projects based on personalised precision medicine (objective 1) and others focused on the development of new advanced therapies and other innovative drugs (objective 2), from which rare diseases could undoubtedly benefit, are envisaged[27]. In fact, approximately 25% (around 291 and 73 million euros of public and private investment, respectively) of the total PERTE budget is allocated to actions and investments under these two objectives[27] (Figure 7, Table 3).

On its part, the PERTE itself emphasizes the need to focus attention on the millions of people with rare and ultra-rare diseases, whose diagnostic and therapeutic possibilities require new knowledge generation and management programs[27]. Likewise, it recognizes that only 8% of the more than 6,000 known rare diseases have an authorized treatment. In this

FIGURE 7. BUDGETS FOR THE PERIOD 2021-2023 OF THE PERTE FOR VANGUARD HEALTH (IN MILLIONS OF EUROS) IN SPAIN




Sources: *own elaboration based on PERTE for Vanguard Health (2022)[27].*

TABLE 3. SUMMARY OF ACTIONS AND INVESTMENTS IN PERSONALIZED MEDICINE AND THE DEVELOPMENT OF ADVANCED THERAPIES AND OTHER INNOVATIVE DRUGS OF SPECIAL RELEVANCE FOR RARE DISEASES IN SPAIN

| Scope of action | Performance | Measure | Public contribution (€, millions) | | | | Private investment (€, millions) |
|---|---|---|---|---|---|---|---|
| | | | 2021 | 2022 | 2023 | Total | |
| **Personalized medicine** | Funding for knowledge generation and transfer in the form of R&D projects | ISCIII Call for Precision Personalized Medicine | 29.5 | 81.5 | - | 111 | - |
| | Incorporation of innovative techniques and technologies in the NHS | Creation of a public-private company to facilitate the availability of advanced therapy and other emerging medicines | - | 36.6 | - | 36.6 | - |
| **Development of advanced therapies and other innovative drugs** | Funding for research projects aimed at drug development in the academic setting (independent clinical research) | ISCIII call for Independent Clinical Research and Advanced Therapies (clinical trials conducted by researchers) | 15 | - | - | 15 | - |
| | Public-private collaboration projects through specific calls for advanced therapies and emerging drugs | CDTI Mission Call for Advanced Therapies and Emerging Medicines (RNA) | 31.2 | - | - | 31.2 | 25 |
| | | Joint ISCIII-CDTI call for proposals in innovation linked to Personalized Medicine and Advanced Therapies | - | 20 | | 20 | 10 |
| | Creation of an R+D+I structure for advanced therapies with a network structure that allows to articulate the existing capabilities throughout the country | Creation and development of the Advanced Therapies Consortium | 7.5 | 15 | - | 22.5 | - |
| | R+D and transfer support platforms | ISCIII platforms to support research (biobanks-biomodels, TIE-MAS, SCREN) | 9 | 9 | - | 18 | - |
| | Co-investment and public-private partnership instrument | Advanced Therapy Medicinal Product (ATMP) commercial company (S-TA) | - | 36.7 | - | 36.7 | 38.2 |
| Total | | | | | | 291 | 73 |

**CDTI**: Centro para el Desarrollo Tecnológico y la Innovación; **I+D+I**: Investigación, Desarrollo e Innovación; **ISCIII**: Instituto de Salud Carlos III; **NHS**: National Health System

Source: *own elaboration based on PERTE for Vanguard Health (2022)*[27].

context, indications for new gene therapy-based drugs are expected, thus making it possible for a large number of these pathologies to be treated with these innovative techniques[27].

Furthermore, under the 2023 General State Budget (PSE), the Ministries of Science and Innovation and Health will allocate an additional 333 million and 300 million euros, respectively, in public investment to this PERTE, bringing its total budget to 2,102 million euros. According to statements from the Ministry of Science and Innovation, this will promote the creation of a high-performance healthcare system based on

precision medicine and advanced therapies through public-private collaboration, in line with what we have seen previously[28].

On the other hand, there are two specific lines of subsidies for RDs included in the Strategic Subsidy Plan (PES) (2021-2023) of the Ministry of Health with the General State Budgets for the year 2021[29] (Table 4):

- The budget item 26.07.313B.454 allocates around 2.8 million euros annually to be transferred to the Autonomous Communities to finance actions aimed at improving epidemiological information on rare diseases and their early detection, as well as the implementation of the strategic lines of the Strategy for Neurodegenerative Diseases of the National Health System (SNS), including Amyotrophic Lateral Sclerosis (ALS).

- The budget item 26.07.313B.484 allocates 18,000 euros to people with hemophilia or other congenital coagulopathies who have developed hepatitis C as a result of receiving treatment with coagulation factor concentrate within the public healthcare system.

TABLE 4. SPECIFIC GRANTS FOR RARE DISEASES INCLUDED IN THE STRATEGIC GRANTS PLAN (2021-2023)

| Grant | Amount (€) | Type of concession | Deadline for achievement |
|---|---|---|---|
| To the Autonomous Communities for strategies against neurodegenerative RDs (including ALS) | 2,818,070 | Direct: nominative | Annual |
| Social assistance for people with hemophilia or other congenital coagulopathies | 18,000 | Direct: established in a regulation with the status of law | Annual |

**ALS:** Amyotrophic Lateral Sclerosis; **RDs:** Rare diseases;

Source: *own elaboration based on the Strategic Grants Plan (2021-2023) (2022)[29].*

## PROPOSALS FOR OPTIMIZING THE BENEFITS OF FUNDS FOR PATIENTS WITH RDS

Budget funds are an essential tool for addressing major development challenges in Europe, as they have the potential to generate significant economic, social, and scientific benefits that enable the transition to a prosperous and sustainable future. The overall objective of the funds is to enhance the competitiveness of both EU member states, associated states, and third countries by primarily financing research, technological development, demonstration, and innovation activities through transnational collaborations between businesses and research institutions[30]. The 2022 European budget includes a number of projects specifically focused on RD research, as well as others that can indirectly benefit individuals affected by these rare conditions[22]. The following are a series of proposals put forward by various stakeholders (healthcare professionals, experts, patients) in the field of RDs, which would help ensure that the funds benefit those affected by these conditions more efficiently in Spain:

**The 2022 budgets of the European funds Horizon Europe and EU4Health will allocate a total of 149 million to projects and programs that directly or directly benefit ODs**

### 1. Streamline the processes of evaluation, financing, and market access:

One of the major challenges facing the EU, particularly Spain, is the development of precision personalized medicine, advanced therapies, and other innovative drugs. A significant portion of public and private funds is allocated to these objectives.

The translation of scientific research into clinical practice has been facilitated through the implementation of certain measures, including the Royal Decree (RD) 1015/2009 on the availability of drugs in special situations. This decree allows patient access to drugs through compassionate use, which involves using the drug before its authorization in Spain. However, off-label uses "shall be exceptional and limited to situations where there are no authorized therapeutic alternatives for a specific patient"[31]. Therefore, in order for innovative drugs to efficiently reach patients, simplification and acceleration of access is necessary to ensure the long-term sustainability of the healthcare system.

In Spain, therapies targeting rare diseases follow the same evaluation and financing process as other drugs. As of August 2022, 85% of the authorized orphan drugs in the EU were marketed in our country. However, only 43% of them were publicly funded, and 47% were funded with restrictions (such as limited indications or indications not covered)[32].

In this regard, it would be interesting to implement best practices from other countries to expedite the evaluation process, such as prioritizing drugs for evaluation and establishing fast-track processes for diseases with significant unmet needs, as is the case in France[33], England[34] and Italy[35]. Furthermore, Italy serves as a reference in financing these types of therapies by establishing specific funds for innovative drugs[36]. Lastly, it is worth mentioning the case of Germany, which allows initial automatic marketing of a drug without prior evaluation during the first year[37].

### 2. Prioritize research efforts and promote public-private collaboration

The fundamental pillar for progress in the field of RDs is to prioritize research, given that 95% of rare diseases have no treatment[38]. To this end, investment should be increased in terms of gross domestic product (GDP), from 1.2% to 2%, as well as fostering public-private collaboration. The Science Pact[39] and the PERTE for Vanguard Health[40] can help to achieve these goals. Specifically, the Plan aims to promote public and private investment in R&D+I, reaching 2.12% of GDP by 2027 and approaching the situation of other EU countries. Achieving this will be a critical factor in ensuring economic growth and boosting the competitiveness and productivity of the Spanish economy. It is worth noting that within the PERTE, there is an objective to promote research in orphan drugs (those intended to treat rare diseases) and ensure their appropriate availability for treatment.

**In Spain, investments in strategic projects for the recovery and economic transformation (PERTE) for the Vanguard Health in personalized medicine and development of advanced therapies and other innovative drugs of particular relevance for rare diseases amount to 364 million for 2021-2023**

### 3. Increased public investment in RDs research

Investment in research is a priority at both European and national levels. However, the development of medicines for certain RDs can be hindered by a lack of funding, mainly due to the limited number of patients, who are also geographically dispersed. As a result, public funds are sometimes insufficient, and it is the patients themselves or their family members who finance the clinical trials in which they will receive the experimental drug[41]. Consequently, experts at the national level are calling for more resources to continue researching RDs and have pointed out that currently, 90% of the research is driven by pharmaceutical companies, with the remaining portion coming from public funds. Additionally, they have highlighted that patient associations serve as a source of support to compensate for the lack of public funding in the research of these conditions[42]. One proposal to address this situation would be to increase public funds, both at the European and national levels, dedicated to research and development of medicines for RDs.

### 4. Increased investment in training

Furthermore, the importance of increased investment in training to address the challenges of advances in innovation is also emphasized[43]. It has been highlighted that Spain is the only country in Europe and the developed world that has not recognized clinical genetics as a medical specialty, leading to an uneven implementation and development of these services in the national healthcare system[44]. For this reason, experts urgently demand the recognition of clinical genetics as a healthcare specialty, as well as other training programs that facilitate learning in the management of these innovative techniques, which would be crucial in accelerating the diagnosis of RDs, as the majority of these conditions have a genetic origin[45]. Additionally, the importance of training and informing family doctors in rare diseases has also been emphasized to facilitate their recognition and comprehensive approach[46].

### 5. Increased healthcare and socio-healthcare investment

To humanize and achieve a comprehensive care for patients with RDs and their families, it would be essential to allocate more funds to the socio-healthcare sector. This would

help alleviate the severe impact that these diseases have not only on a social level but also in terms of the personal and familial economy of the patients. Socio-healthcare interventions play an important role in delaying the onset of dependency, and when dependency is already present, healthcare support is essential for the person's proper adaptation to the situation and to improve their quality of life[47]. Regarding healthcare infrastructure for RDs, investments should be increased, with consideration given to their territorial distribution so as to promote accessible care without excessive resource dispersion[38].

In conclusion, experts in the field of RDs have advocated for the need to persevere in initiatives that improve all aspects of rare diseases, from research to diagnosis and treatment. Despite the low prevalence of RDs, they have a significant impact on the lives of patients and their families, making it crucial to have a healthcare system with less bureaucracy, faster diagnostic processes, and increased investment in effective treatments[48].

**It is important to invest in ODs, in a coordinated and planned way, to achieve synergies and adapt research to the needs of patients and their families**

In this article, we have reviewed how funds, whether European or national, have contributed to promoting research and development activities that foster key healthcare policies to make innovative therapies accessible and improve the lives of patients with RDs. It also aims to raise awareness and knowledge about these conditions. The central idea of the article is to emphasize the importance of continued investment in these diseases in a coordinated and planned manner, to achieve synergies and align research with the needs of patients and their families.



1. European Commission. Rare diseases. [accedido 14 noviembre 2022]. Available from: https://health.ec.europa.eu/non-communicable-diseases/steering-group/rare-diseases_en.
2. Groft SC, Posada M, Taruscio D. Progress, challenges and global approaches to rare diseases. Acta Paediatr Oslo Nor 1992. 2021;110(10):2711-6, doi: 10.1111/apa.15974.
3. Orphanet. Orphanet in numbers. 2020.
4. European Commission, Directorate-General for Research and Innovation. Rare diseases: a major unmet medical need. LU: Publications Office of the European Union; 2017.
5. European Organisation for Rare Diseases (EURORDIS). 20 Years of Achievements in the Rare Disease Community. 2017.
6. European Commission, Directorate-General for Research and Innovation-European Commission. Collaboration: a key to unlock the challenges of rare diseases research. LU: Publications Office of the European Union; 2021.
7. European Commission. Research Projects under Framework Programmes. [accedido 15 noviembre 2022]. Available from: https://ec.europa.eu/eurostat/cros/content/research-projects-under-framework-programmes-0_en.
8. European Commission. R&I Projects - Key Figures. [accedido 17 noviembre 2022]. Available from: https://webgate.ec.europa.eu/dashboard/sense/app/98dcd94d-ca66-4ce0-865b-48ffe7f19f35/sheet/KVdtQ/state/analysis.
9. European Commission. Development of Community research - commitments 1984 - 2013.
10. European Commission. Horizon 2020. [accedido 17 noviembre 2022]. Available from: https://research-and-innovation.ec.europa.eu/funding/funding-opportunities/funding-programmes-and-open-calls/horizon-2020_en.
11. European Commission. Horizon Europe. [accedido 17 noviembre 2022]. Available from: https://research-and-innovation.ec.europa.eu/funding/funding-opportunities/funding-programmes-and-open-calls/horizon-europe_en.
12. European Commission. EU research on rare diseases. [accedido 16 noviembre 2022]. Available from: https://research-and-innovation.ec.europa.eu/research-area/health/rare-diseases_en.
13. European Commission. FET Open. [accedido 22 noviembre 2022]. Available from: https://cordis.europa.eu/programme/id/H2020-EU.1.2.1./es.
14. European Commission. Marie Skłodowska-Curie Actions: Developing talents, advancing research. [accedido 17 noviembre 2022]. Available from: https://marie-sklodowska-curie-actions.ec.europa.eu/.
15. European Commission. European Research Infrastructures. [accedido 16 noviembre 2022]. Available from: https://research-and-innovation.ec.europa.eu/strategy/strategy-2020-2024/our-digital-future/european-research-infrastructures_en.
16. European Commission. European Innovation Council. [accedido 22 noviembre 2022]. Available from: https://eic.ec.europa.eu/index_en.
17. European Commission. European Research Council. [accedido 22 noviembre 2022]. Available from: https://erc.europa.eu/homepage.
18. Centro para el Desarrollo Tecnológico Industrial (CDTI), Fundación Española para la Ciencia y la Tecnología (FECYT), Ministerio de Ciencia e Innovación (MCIN). Guía rápida de Horizonte Europa. 2022.
19. European Commission. UEproSalud 2021-2027: a vision for a healthier European Union. [accedido 15 noviembre 2022]. Available from: https://health.ec.europa.eu/funding/eu4health-programme-2021-2027-vision-healthier-european-union_es.
20. European Commission. Horizon Europe - Work Programme 2021-2022 Health. 2022.
21. European Commission. ANNEX II to the Commission Implementing Decision amending Implementing Decision C(2021) 4793 final of 24 June 2021 and Implementing Decision C (2022) 317 final of 14 January 2022 on the financing of the Programme for the Union's action in the field of health ('EU4Health Programme') and the adoption of the work programmes for 2021 and 2022 respectively. 2022.
22. European Commission. CORDIS | EU research results. [accedido 15 noviembre 2022]. Available from: https://cordis.europa.eu/search?q=contenttype%3D%27project%27%20AND%20(%27rare%27%20AND%20%27diseases%27)&p=1&num=100&srt=Relevance:decreasing.
23. European Commission. Funding & tender opportunities - Single Electronic Data Interchange Area (SEDIA). [accedido 18 noviembre 2022]. Available from: https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/opportunities/horizon-dashboard.
24. Remedi4All - The european platform for medicines repurposing. [accedido 2 diciembre 2022]. Available from: https://remedi4all.org/.
25. Roessler HI, Knoers NVAM, van Haelst MM, van Haaften G. Drug Repurposing for Rare Diseases. Trends Pharmacol Sci. 2021;42(4):255-67, doi: 10.1016/j.tips.2021.01.003.



26. Gobierno de España. ¿Qué son los PERTE? [accedido 2 diciembre 2022]. Available from: https://planderecuperacion.gob.es/preguntas/que-son-los-perte.

27. Gobierno de España. PERTE para la salud de vanguardia. [accedido 2 diciembre 2022]. Available from: https://planderecuperacion.gob.es/como-acceder-a-los-fondos/pertes/perte-para-la-salud-de-vanguardia.

28. La Moncloa. 07/10/2022. El Ministerio de Ciencia e Innovación cuenta en 2023 con el mayor presupuesto en I+D+i de la historia de nuestro país. [accedido 2 diciembre 2022]. Available from: https://www.lamoncloa.gob.es/serviciosdeprensa/notasprensa/ciencia-e-innovacion/Paginas/2022/071022-morant-pge-2023.aspx.

29. Ministerio de Sanidad. Plan Estratégico de Subvenciones (2021-2023). 2022.

30. Ministerio de Hacienda y Función Pública. Programa Marco de I+D. [accedido 5 diciembre 2022]. Available from: https://www.fondoseuropeos.hacienda.gob.es/sitios/dgfc/es-ES/paginas/pmid.aspx.

31. Ministerio de Sanidad y Política Social. Real Decreto 1015/2009, de 19 de junio, por el que se regula la disponibilidad de medicamentos en situaciones especiales. 2009.

32. Asociación Española de Laboratorios de Medicamentos Huérfanos y Ultrahuérfanos (AELMHU). Segundo informe cuatrimestral de acceso a los medicamentos huérfanos en España 2022. 2022, Available from: https://aelmhu.es/informes-de-acceso/.

33. Agence nationale de sécurité du médicament et des produits de santé (ANSM). Essais cliniques: Procédure Fast-track pour les médicaments. [accedido 5 diciembre 2022]. Available from: https://ansm.sante.fr/page/essais-cliniques-procedure-fast-track-pour-les-medicaments.

34. NHS England. NHS England announces new Innovative Medicines Fund to fast-track promising new drugs. [accedido 22 diciembre 2021]. Available from: https://www.england.nhs.uk/2021/07/nhs-england-announces-new-innovative-medicines-fund-to-fast-track-promising-new-drugs/.

35. Agenzia Italiana del Farmaco (AIFA). Farmaci innovativi. [accedido 9 junio 2021]. Available from: https://aifa.gov.it/farmaci-innovativi.

36. Gobierno de Italia. Ley no 232 del 11 dicembre 2016 sobre Presupuesto estatal para el año 2017 y presupuesto plurianual para el trienio 2017-2019. [accedido 15 junio 2021]. Available from: https://www.gazzettaufficiale.it/eli/id/2016/12/21/16G00242/sg.

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

38. Sobi. 33 propuestas para mejorar la atención, cuidado y calidad de vida de los pacientes con enfermedades raras - La Humanización en las Enfermedades Raras. 2022.

39. Ministerio de Ciencia e Innovacióne. Pacto por la Ciencia y la Innovación. [accedido 5 diciembre 2022]. Available from: https://www.ciencia.gob.es/Estrategias-y-Planes/Estrategias/Pacto-por-la-Ciencia-y-la-Innovacion.html;jsessionid=-C33731A3E20C2E166EE6F40DBE23AC92.2.

40. Gobierno de España. Plan de Recuperación, Transformación y Resiliencia. 2021.

41. Dal-Ré R, Palau F, Guillén-Navarro E, Ayuso C. Ensayos clínicos en enfermedades raras financiados por los participantes. An Pediatría. 2020;93(4):267.e1-267.e9, doi: 10.1016/j.anpedi.2020.03.019.

42. El Mundo. Los expertos reclaman recursos para seguir investigando las enfermedades raras. [accedido 5 diciembre 2022]. Available from: https://www.elmundo.es/extras/2022/11/23/6375ac11fdddffa93b8b458e.html.

43. Desayuno POP sobre «Nuevos paradigmas en investigación clínica: un compromiso de todos los agentes». 2022.

44. Redacción Médica. Designar genética clínica como especialidad, clave en enfermedades raras. [accedido 9 diciembre 2022]. Available from: https://www.redaccionmedica.com/secciones/industria/designar-genetica-clinica-como-especialidad-clave-en-enfermedades-raras-9236.

45. Orphanet. Activity Report. 2019.

46. Ipsen España. El reconocimiento de la genética clínica como especialidad y la gestión coordinada de los datos a nivel nacional, claves para acelerar el acceso de los pacientes con EERR al diagnóstico. 2022, Available from: https://www.ipsen.com/spain/blog/2022/02/23/el-reconocimiento-de-la-genetica-clinica-como-especialidad-y-la-gestion-coordinada-de-los-datos-a-nivel-nacional-claves-para-acelerar-el-acceso-de-los-pacientes-con-eerr-al-diagnostico/.

47. Avellaneda A, Izquierdo M, Torrent-Farnell J, Ramón JR. Enfermedades raras: enfermedades crónicas que requieren un nuevo enfoque sociosanitario. An Sist Sanit Navar. 2007;30(2):177-90.

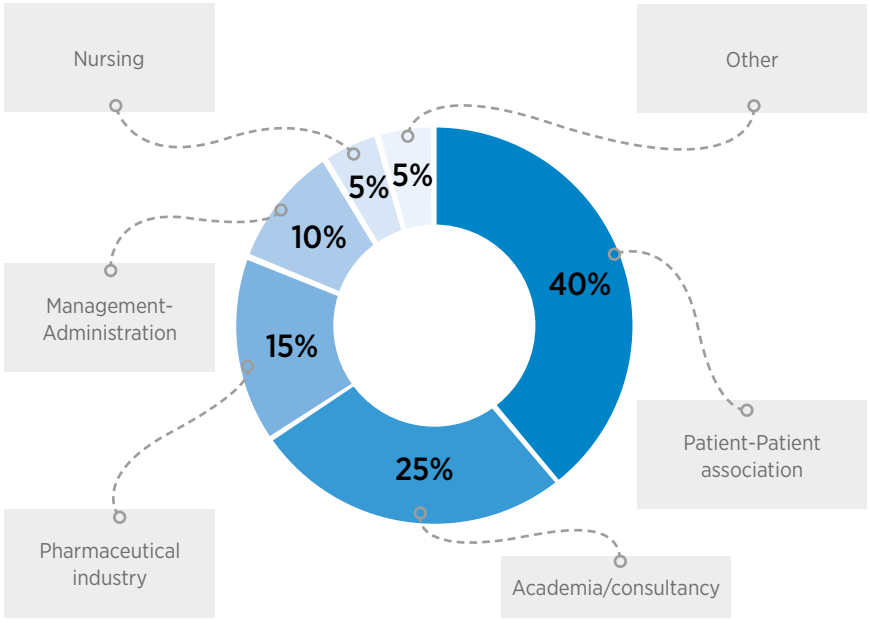
48. La Moncloa. 12/05/2022. Sanidad avanza hacia la homogenización del acceso a las pruebas genéticas en todo el territorio para el diagnóstico, tratamiento y seguimiento de las enfermedades rara. [accedido 7 diciembre 2022]. Available from: https://www.lamoncloa.gob.es/serviciosdeprensa/notasprensa/sanidad14/Paginas/2022/120522-darias-enfermedades-raras.aspx.

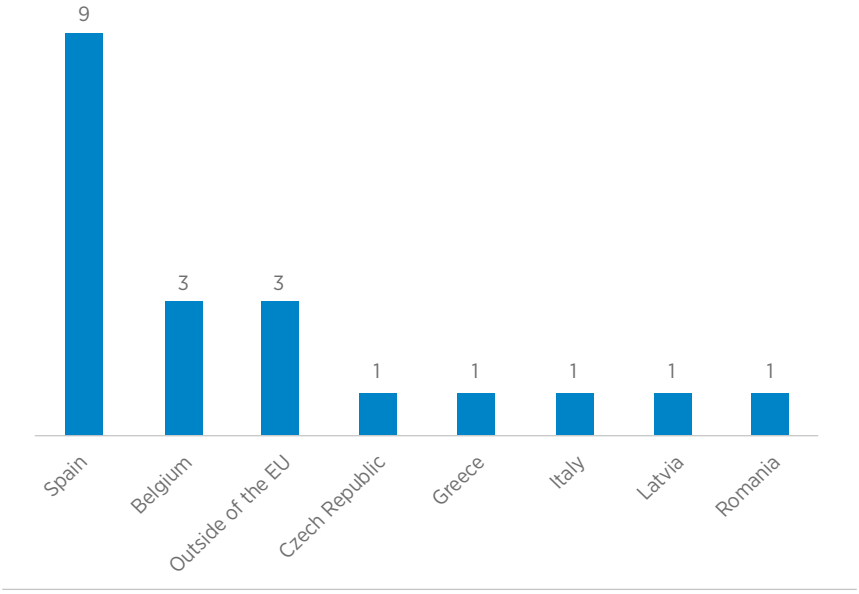
# INNOVATIVE FINANCING MODELS AND CASES THAT HAVE TRANSFORMED THE LIVES OF PATIENTS AND FAMILIES WITH RARE DISEASES (RDs)

*newsRARE Editorial Board*

The aim of this barometer is to gain insight into the perspectives of a wide range of stakeholders in the healthcare sector regarding innovative financing models within the realm of RDs and the potential success stories that have had a positive impact on the lives and environments of RD patients. To achieve this objective, the editorial board at newsRARE created a tailored electronic survey, which was distributed to a database of individuals connected to the RD community. The survey was accessible from 19th May to 17th September 2023.

A total of 20 individuals participated in the survey, with the following breakdown of roles: 8 (40%) were patients or represented patient associations, 5 (25%) were academics and consultants, 3 (15%) were affiliated with the pharmaceutical industry, 2 (10%) were professionals in management and public administration, 1 (5%) were nursing staff, and 1 (5%) came from diverse fields. The primary professional activities of the respondents were predominantly centred in Spain (n=9; 45%), with Belgium following closely behind (n=3; 15%). Additionally, there was representation from five other EU countries, each with one



respondent. Furthermore, three respondents (15%) originated from countries outside the EU.

The survey had two main parts. Firstly, it asked about innovative financing models for RD drugs in Europe, including stakeholders, financing methods, monitoring systems, and the future outlook. Secondly, it explored the significance of sharing success stories in the RD field and gathered opinions on collaboration among the public, healthcare professionals, and administrations/industry for RD achievements. Participants were also invited to share their own success stories.

## PART I: INNOVATIVE FINANCING MODELS

### Leadership and implementation level

The survey findings reveal that a plurality of respondents, constituting 32% of the responses, are in favour of government or state agencies taking the lead in implementing innovative models for RD drugs. In contrast, 27% of respondents advocate for European or international coordinating bodies to spearhead these initiatives, while 23% believe that the pharmaceutical industry itself should assume a leading role. Only a minority of respondents, specifically 10% and 8%, suggest that regional health services and healthcare providers (hospitals) should take on leadership roles in this process, respectively. It's noteworthy that members of academia/consultants and the pharmaceutical industry have shown slightly above-average support for the pharmaceutical industry, with 30% to 33% expressing a stronger belief in the pharmaceutical industry role as one of the key stakeholders in initiating this process.

On the other hand, an overwhelming majority of the respondents (70%) advocate for a centralized implementation of this type of agreements at the European/International level, while the remaining 30% believed it should be done at the National level. None of the respondents believe it should be done at the regional (State/Province) or local level (Hospital) (FIGURE 1).

### The most suitable types of agreement

Eighteen out of twenty respondents (90%) believe that innovative outcome-based models in healthcare are the most suitable for RD drugs, compared to only 10% (n=2) who think that financial outcome-based contracts should be preferred (FIGURE 2).

FIGURE 2. TYPES OF INNOVATIVE MODELS MOST SUITABLE FOR FINANCING IN THE RD FIELD

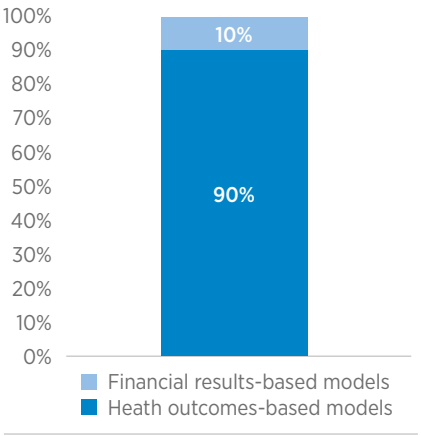
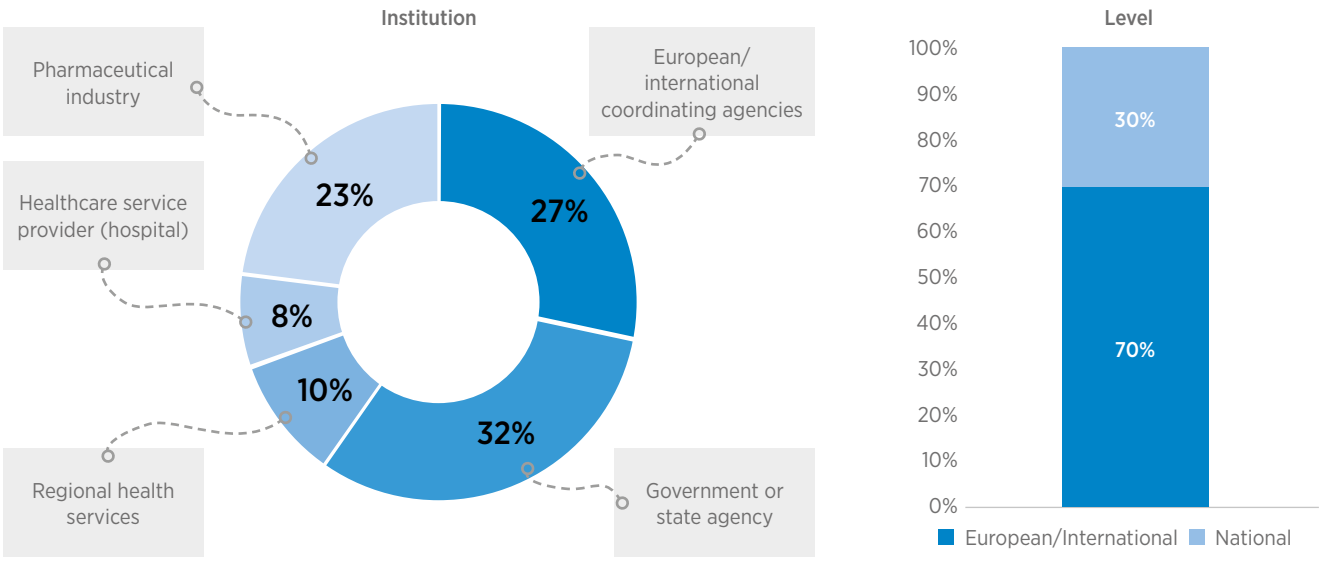



FIGURE 1. INSTITUTION FROM WHICH THE INITIATIVE TO IMPLEMENT INNOVATIVE RD FINANCING MODELS MUST ORIGINATE AND THE LEVEL AT WHICH THEY MUST BE IMPLEMENTED, %



On the other hand, there is no consensus on which type of contract is most suitable in each category. Within health outcome-based agreements, 32% believe that the most suitable type is agreements based on cost-effectiveness, while 25% believe it is coverage contracts under evidence-seeking, followed by 23% advocating for agreements based on final clinical outcomes, and 20% for intermediate clinical outcomes. In the category of financial outcome-based agreements, market entry agreements and discounts-refunds-free medications would be the most suitable agreements (28% each), followed by price-volume (24%) and expenditure ceilings (20%).

### Advantages and disadvantages

The primary advantage of innovative models, as per the viewpoint of 28% of the respondents, is their potential to streamline and accelerate entry into the pharmaceutical market. Following this, they can also mitigate the inherent uncertainty associated with introducing new drugs (18%) and enable the ongoing collection of relevant data from routine clinical practice (15%).

Conversely, the chief drawback of these models stems from the necessity for intricate negotiations between payers and the pharmaceutical industry to bring them to fruition, as indicated by 30% of respondents. Additionally, their implementation hinges on the presence of robust information systems (18%), and the decentralization of healthcare decision-making raises questions about the allocation of responsibilities for negotiating, managing, monitoring, and financing these agreements (18%). One respondent commented that innovative models are less transparent than tenders and positive lists (TABLE 1).

### Current and future use

90% of the respondents believe that the current utilization of innovative financing models in the field of RD drugs is less than desirable. 10% believe that its usage is adequate, while no one believes it is more than desirable. In contrast, the vast majority (80%) agree that its future use (in the next 5 years) will be greater than the current one, while 20% believe it will remain the same as it is now. No one believes it will be lower (FIGURE 3).

### The imperative of information systems

Eight out of ten survey participants (80%) hold the view that information systems or tracking applications are indispensable for the successful implementation of innovative funding models for RD. Conversely, 15% of respondents find them to be a favourable addition, while a mere 5% deem them superfluous. Meanwhile, in the perspective of the surveyed individuals, 50% advocate the development of enhanced information systems at the national level, with 35% favouring an European approach. Only 10% and 5% believe such systems should be established at the regional or hospital level, respectively (FIGURE 4).

TABLE 1: ADVANTAGES AND DISADVANTAGES OF FINANCING MODELS FOR ORPHAN DRUGS, %

| ADVANTAGES | % |
|---|---|
| They can facilitate and accelerate access to the drug market | 27.5 |
| They reduce the inherent uncertainty in introducing new drugs | 17.5 |
| They allow for the collection of relevant data from routine clinical practice in a continuous manner | 15.0 |
| They can result in a real improvement in system efficiency | 12.5 |
| They can increase the sustainability of the system | 12.5 |
| They promote the appropriate selection of patients who can truly benefit from treatment | 7.5 |
| They encourage a new type of relationship between administration and industry | 7.5 |
| **DISADVANTAGES** | **%** |
| Complex negotiations must be carried out between the payer and the pharmaceutical industry | 30.0 |
| Their implementation requires the existence of powerful information systems | 17.5 |
| Decentralization in healthcare decision-making raises questions about who should be responsible for negotiating, managing, monitoring, and financing these agreements | 17.5 |
| Not all treatments will have a specific, objective, and relevant outcome measure | 12.5 |
| They entail significant administrative, structural, and financial costs | 10.0 |
| They involve a significant bureaucratic burden | 7.5 |
| Other | 5.0 |

FIGURE 3. PERCEPTIONS REGARDING THE CURRENT AND FUTURE (5 YEARS) USE OF INNOVATIVE RD FINANCING MODELS

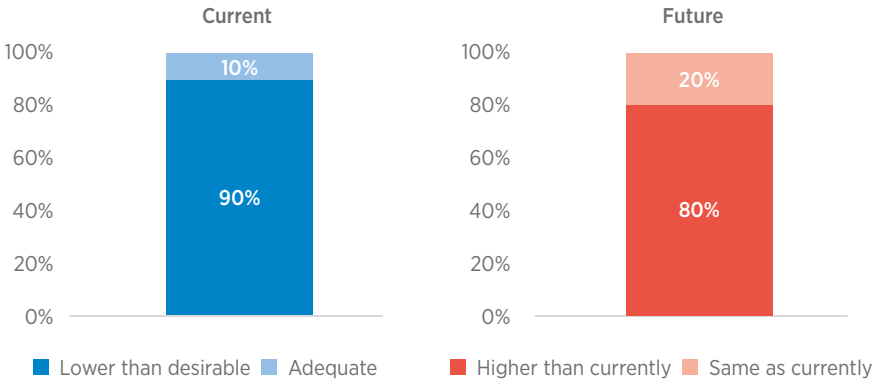
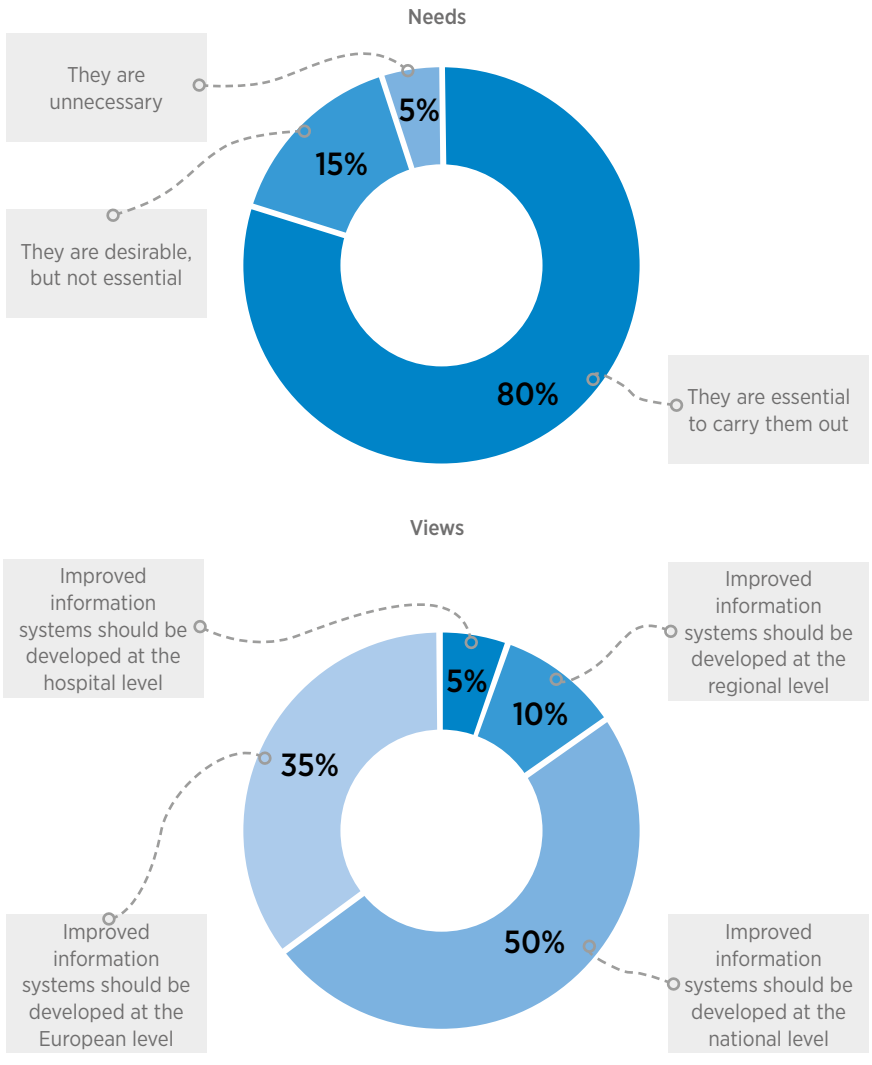



FIGURE 4. NEEDS AND VIEWS ON INFORMATION SYSTEMS FOR TRACKING INNOVATIVE FINANCIAL AGREEMENTS ON RD




## PART II: CASES THAT HAVE TRANSFORMED THE LIVES OF PATIENTS AND FAMILIES

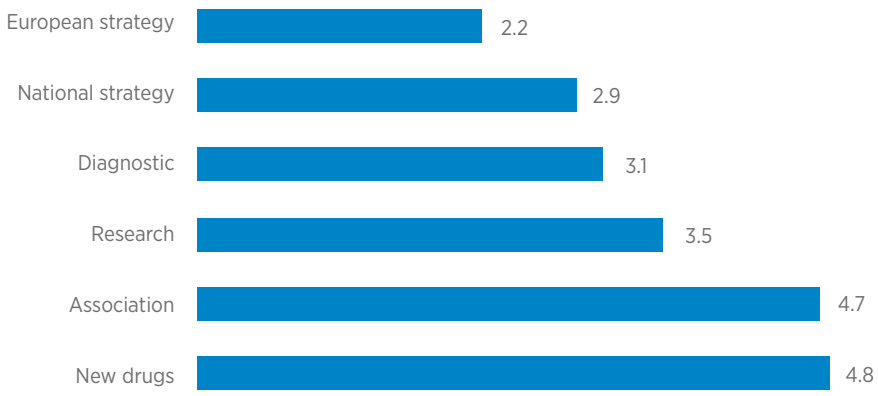
### Ranking of success cases

In the first question of the second segment of our survey, we asked respondents to rank 6 predefined cases of success in RD in order to understand their relative importance. According to their responses, the implementation of a RD strategy at the European level (2.2 out of 6, where 1 represents the most important case and 6 the least important), the implementation of a national-level RD strategy (2.9), and the existence of a new diagnostic method enabling the rapid discovery of new RDs (3.1) are the top three cases that would represent the most significant successes (FIGURE 5).

### Benefits of showcasing success stories

When asked to rank five predefined aspects related to the positive outcomes resulting from increased visibility of success cases in RD, between 65% and 90% of the respondents indicated that their primary utilities are to serve as a reference for the implementation of best practices at the clinical (micro), management (meso), and policy (macro) levels, as well as a motivation to keep improving. On the other hand, greater visibility of success cases would also be useful for the generation of greater knowledge and social awareness and as a recognition for the individuals responsible for each case, even though the majority (55% and 80%) of the respondents ranked them as the two least useful aspects (FIGURE 6).

FIGURE 5. RANKING OF DIFFERENT SUCCESS CASES PROPOSED (AVERAGE)




**Notes:** Interpretation of average data: **1** = first position as the case with the highest relative success; **6** = last position. **European Strategy**: Implementing a RD strategy at the European level. **Diagnosis**: A new diagnostic method that allows for the rapid discovery of new RDs. **National Strategy**: Implementing a RD strategy at the national level. **Research**: Connecting different RD research groups to generate various synergies. **New Drugs**: Launching a new medication that improves the survival of a very small group of patients. **Association**: Creating a new patient association that brings together individuals with the same ultra-rare disease at the national level.

## Coordinated efforts

A fundamental aspect for achieving successful cases in RD is the implementation of coordinated efforts among the general population, healthcare professionals, healthcare administration, and industry. In this regard, the respondents believe that there is a lot of room for improvement. On a scale of 0 to 10 (where 0 represents "no coordination effort made" and 10 represents "a lot of coordination effort"), the average of the responses was 4.4, indicating a moderate level of coordination effort.

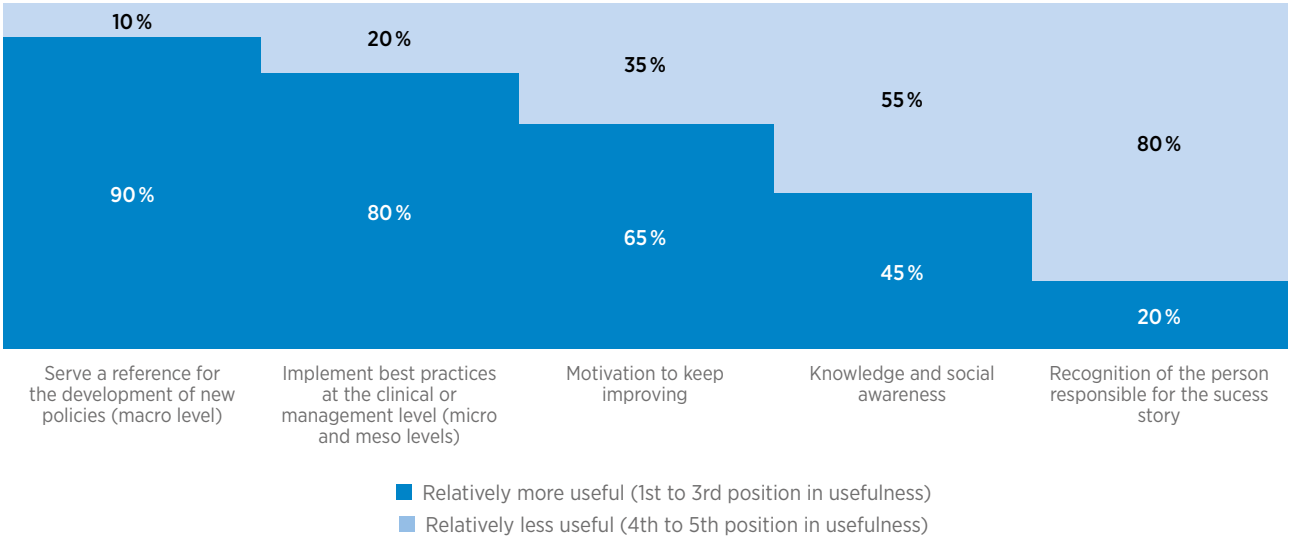
## Specific success cases

In the last question of the survey, respondents were asked, through open-ended questions, to specify experiences they considered successful in the areas of diagnosis, treatment, research, technology, integrated care, and political, regulatory, and associative context, following their own criteria of success (subjectivity). These experiences could have occurred at both individual and institutional, national, or community levels. Below, we present these results.

### Diagnosis and treatment

- Genomic diagnostic techniques have been introduced, enhancing disease diagnosis.
- Early diagnosis and investment in research and innovation are crucial for RD patients' quality of life.
- National alliances played a role in including genetic testing in national plans for various RD.

FIGURE 6. THE BENEFIT OF INCREASED VISIBILITY OF RD SUCCESS CASES



- Treatments for spinal muscular atrophy (SMA) have profoundly impacted affected individuals.

### Research, integrated care and technology

- RD have gained more visibility due to advancements in research and technology.
- A publication recommending holistic care for Hereditary Transthyretin Amyloidosis, aiming to improve its international approach.

### Political and regulatory

- European legislation for Orphan Medicine Products in 2000 incentivized innovation.
- Continued support and listening to patient needs by the EU Commission are crucial.

### Associative context

- Patient associations and organizations now have a stronger voice advocating for unmet needs.
- The Cross-border Health Care Directive and ERN organization have transformed care for RD patients in Europe.
- The Columbus Children Foundation has facilitated access to treatment for some children.

## KEY MESSAGES

**PART I: Innovative financing models**

- Survey respondents are divided on who should lead the implementation of innovative models for RD drugs, with 32% favouring government agencies, 27% supporting international bodies, and 23% endorsing the pharmaceutical industry.
- The majority (70%) of respondents prefer a centralized approach at the European/International level for these agreements, while 30% opt for national-level implementation, with no support for regional or local levels.
- 90% of respondents prefer innovative health outcome-based models for RD drugs, with only 10% favouring financial outcome-based contracts.
- There is no consensus on the preferred specific type of contract within each category, but for health outcome-based agreements, cost-effectiveness agreements and coverage contracts under evidence-seeking are the top choices, while for financial outcome-based agreements, market entry agreements and discounts-refunds-free medications are favoured.
- The key advantage of innovative models is that it streamlines and accelerates entry into the pharmaceutical market (28% of responses), while the key drawback of those models relates to the need of intricate negotiations between payers and the pharmaceutical industry (30%).
- 90% of respondents find that current RD drug financing models implementation level is lower than desirable, while 80% expect future use to increase in the next 5 years, with no one anticipating a decrease.

**PART II: cases that have transformed the lives of patients and families**

- Respondents ranked the top three cases of success in RD as: European-level RD strategy (2.2 out of 6, where 1 represents the mostimportant case and 6 the least important), national-level RD strategy (2.9), and rapid discovery of new RDs via diagnostic methods (3.1)
- Between 65% and 90% of the respondents indicated that the primary utility of increased visibility of success cases in RD are to serve as a reference for the implementation of best practices at the clinical (micro), management (meso), and policy (macro) levels, as well as a motivation to keep improving.
- The coordination effort among the general population, healthcare professionals, administration, and industry are considered as moderate (4.4/10).

# CLINICAL DEVELOPMENT INNOVATION IN RARE DISEASES: LESSONS LEARNED AND BEST PRACTICES FROM THE DEVELOPAKURE CONSORTIUM

*Mattias Rudebeck, Ciarán Scott, Nicholas P. Rhodes, Christa van Kan, Birgitta Olsson, Mohammed Al-sbou, Anthony K. Hall, Nicolas Sireau. Orphanet Journal of Rare Diseases 2021; 16,510*

**INDALECIO CORUGEDO DE LAS CUEVAS**

*President of the Advisory Council, Weber Foundation*

## SUMMARY

Recently, there have been numerous opportunities for the development of therapies for rare diseases (RDs). However, there is no organizational framework that integrates the different individual initiatives, some of which are very interesting.

The article being discussed presents a proposal for a model to create a single consortium that identifies and includes some of the most relevant aspects of the latest developments in rare disease (RD) research. The proposed project is called DevelopAKUre, and its main contribution involves the aggregation of contributions from the main agents involved in the development of pharmaceutical products for RDs, such as academia, industry, and patient associations.

The proposal suggests that equal contributions from these agents in the consortium would guarantee success in generating a new organizational culture in which all participants have the same incentives for the proper development of the program.

## 1. Current status of global treatment of RD

- There are over 7,000 RDs that affect more than 400 million people worldwide. Unfortunately, approximately 95% of these RDs do not have an approved treatment.
- One of the main reasons for this is the lack of adequate knowledge of the biology of RDs.
- Another significant reason is the design and development of clinical studies with very small patient samples. Often, these samples are located at a great distance, making recruitment and communication very difficult.

- However, even when recruitment is achieved, a negative factor is the continuity over time of individuals in the sample.

- Until now, there has been a lack of specialized centers for the care of patients with RDs.

- Another decisive factor in the development of research and treatment for other diseases has been the creation and development of patient organizations. However, this process is still very incipient in the case of RDs, given their high number, clinical heterogeneity, and complicated geographic distribution, which makes it very challenging.

- Finally, the contribution of the clinical academic world in terms of providing input for research and personnel to carry it out has not been appreciable thus far in obtaining a good joint result.

## 2. A new European experience (DevelopAKUre)

The article being discussed presents a series of conclusions derived from the presentation of a collaborative model for the development and treatment of a rare genetic disease known as alkaptonuria (AKU). This disease affects 1 in 250,000 to 1,000,000 people, and the clinical process that characterizes this pathology is called ochronosis. It has a slow development in the early years of the individual, with very destructive and acute development at the end of their twenties.

The study focuses on the requirement for the final objectives of the set of factors mentioned above. The grouping of these factors in the study was as follows:

- Clinical knowledge of the pathology was derived from various research processes that defined its evolution in patients.

- In parallel with the above, the first group of patients (AKU Society, UK) was created, along with two other groups. On the one hand, the Clinical Experts Group (Royal Liverpool University Hospital, UK) acted as the consortium coordinator, and on the other hand, the Group of Academic Researchers (University of Liverpool, UK) was established.

- In total, 12 organizations were recruited from the above centers to form the Consortium, founded in 2012 and named DevelopAKUre (developacure). Strong consortium leadership allowed for efficient communication and rapid resolution of issues.

- The consortium received external funding from the European Commission, which covered part of the costs of the clinical development program of the project. The costs were distributed equitably among the different participants in the program, who established a rigid participation contract prior to the start of the work. The solution of external financing was a significant step in resolving the very heterogeneous financing systems that have always been a great obstacle for RD cases.

- The recruitment of patients has been the main objective of the AKU Society, founded in 2003. Initially, recruitment was carried out with patients from the United Kingdom, but due to the low number of people affected by the disease, it was extended to other European countries, which brought about displacement and management problems. To recruit, retain and ensure continuity of patient samples, the generation of strong incentives (advocacy) has been an essential factor to generate and educate. This required good cross-sectional communication between the different groups.

- Good coordination among academic institutions, healthcare facilities, patient organizations, and the pharmaceutical industry is crucial to achieve the common goal of researching new therapies. The most important tasks within these decision centers include designing the study and operational plan, recruiting and retaining patients, and ensuring effective communication and information exchange. Establishing a strong incentive system for patient recruitment is also critical to the success of the program, as previously mentioned.

## COMMENT

As an economist, I appeal to the philosophy of one of the classic economists of the last century, Ronald Coase, who summarizes his vision of research in the economic world as follows: "Progress in interpreting the functioning of an economic system comes from the game between theory and empirical work. The theory suggests what empirical work can be productive. The corresponding empirical work will then suggest the modification to be made in the theory, which will then imply the subsequent creation

of a new empirical work. In this way, scientific research is an endless process that will provide new knowledge at each stage".

Coase developed a theory about the meaning and functioning of a company run by an entrepreneur in his publication "The Nature of the Firm" (Economica, 1937). The ultimate goal of the entrepreneur is to reduce transaction costs, which can be enormous if decisions are not centralized. Concentration and coordination in decision-making increase productivity and reduce costs. This interpretation is continuously applicable in the economic system, justifying the appearance of banks in the financial world, schools and universities in education, and hospitals and primary care centers in the health sector. Thus, this provides a first justification for the creation of the consortium being explained here. In making a final balance of requirements for the organizational system we define here, we can summarize based on the following conclusions:

1. Equal (equitable) participation of all parties involved, as described above. A project board should be established to oversee the process. The ultimate goal is to establish a modus operandi or culture that allows for the execution of various programs within a pre-established period of time.

2. This organization assumes that its members have a strong presence in both space and time, which translates into a commitment to participate. This is equivalent to the existence of certain property rights of the members of the consortium, in which strong leadership coexists on one hand, and continuous communication among its members on the other. From here, the generation of a system of incentives, both monetary and non-monetary, is necessary to lead the development of the program towards the final objective.

3. The previous point proposes a financing model for the consortium that is not limited only to the interactions between the different actors in the system.

4. It seems that some approaches, such as those presented here, are still foreign in our country when it comes to proposals for treatments on rare diseases (RD) and orphan drugs (OD). There is still a lot to be done. There really needs to be a system of incentives for this and an even better recognition of the economist's role in health research, which should not be limited to evaluating specific cases but rather shedding light on a philosophy that explains individual performance in a world where scarcity is the main constraint.

5. The article cited supports the statement above.

6. Table 2 in the article provides an excellent summary of the factors to consider in collaborative projects among the pharmaceutical industry, academia, and patient associations for analyzing the development of a certain disease and its corresponding pharmacological treatment.

**There is a need for a system of incentives and better recognition of the role of economists in health research. This recognition should not be limited to the evaluation of specific cases**

# IMPLEMENTING RISK-SHARING ARRANGEMENTS FOR INNOVATIVE MEDICINES: THE EXPERIENCE IN CATALONIA (SPAIN)

*Laura Guarga, Montse Gasol, Anna Reyes, Marta Roig, Enric Alonso, Ana Clopés, Joaquim Delgadillo, Value in Health (2022); 25(5):803–809*

**ANTONI GILABERT PERRAMON**

*Director of Innovation and Partnership Consorci de Salut i Social de Catalunya*

**SUMMARY**

The objective of this study is to describe the various types of risk-sharing agreements implemented in Catalonia (Spain), and to provide a detailed description of the economic and health outcomes achieved through them.

To achieve this, we reviewed the agreements signed by Catsalut and the hospitals in the Catalan health system with pharmaceutical laboratories between January 2016 and December 2019. We conducted a retrospective analysis of the information contained in the registry of patients and outpatient medication dispensing treatments in hospitals. Specifically, we analyzed the number of agreements implemented, their duration, the number of medications and diseases involved, and the reasons for their ending.

The agreements were categorized based on the risk they aimed to mitigate and could be classified as either agreements related to health outcomes (performance-based risk-sharing agreements, PBRSA) or cost-sharing agreements (CSA).

During the analyzed period, Catsalut implemented a total of 15 agreements, out of which 10 were still in progress at the time

of analysis (2020). The first agreement was signed in 2016, followed by five in 2017, five in 2018, and four in 2019. These agreements involved 14 different treatments, with the majority (n=11) being for oncohematological diseases, followed by rare diseases (n=3) and neurological diseases (n=1). Negotiations were held with 11 different pharmaceutical companies. Among the agreements implemented, eight were based on health outcomes, while seven were cost-sharing agreements.

The main results achieved are summarized below:

**PBRSA:**

- In all of the agreements, Catsalut paid the reimbursement price for the treatment in advance, and the laboratory agreed to pay the entire cost in those patients who did not achieve the intermediate clinical objectives defined in the agreement.
- Evaluations were conducted at 2 and 24 weeks.
- One of these agreements involved the participation of 8 out of the 65 hospitals in the Catalan health system.
- During the analyzed period, 73% of the 951 participating patients achieved the established objectives, although the percentages ranged from 13% in urothelial cancer to 94% in breast cancer.
- The total cost of drugs included in these agreements during the analyzed period was 9,295,755 euros, of which 11% (1.03 million euros) was reimbursed to Catsalut.

**CSA:**

- Among these economic results agreements, two discount agreements, three spending ceiling agreements, and two price-volume agreements were made.
- A total of 2,066 patients were treated under these agreements in 26 out of the 65 hospitals in the Catalan public health system. Of these, 42% were treated for lung cancer, 42% for multiple myeloma, 6% for rare renal diseases, 5% for rare respiratory diseases, 4% for rare gastrointestinal diseases, and 1% for melanoma.
- The mean age of the patients included in these agreements was 67 years (range: 14 to 93 years), and 37% of them were women.
- During the analyzed period, the total cost of drugs included in these agreements was 51,689,728 euros, out of which 2.61% (1.35 million euros) was reimbursed to Catsalut.

## COMMENT

This is one of the few studies published in Spain that provides real data on the risk-sharing agreements implemented in practice. As noted by the authors of the paper, all of these agreements belong to the Catalan public health system. While there is a relatively abundant literature on this type of agreement from a conceptual or terminological perspective, there are very few publications that evaluate the achieved results. Such evaluations are necessary to better understand the need for these agreements and to improve their design in the future.

Risk-sharing agreements are primarily established for medicines with high levels of uncertainty and potential for significant clinical and/or economic implications. Therefore, they are particularly applied to oncohematological therapies and rare or minority diseases (RD).

Infact, according to this study, 3 of the 15 agreements implemented in Catalonia were focused on rare or minority diseases (in gastroenterology, nephrology and respiratory), and all of them were agreements based on economic results. Thus, 20% of the RSAs implemented were in RD. However, in all three cases, uncertainty was related to either the number of patients to be treated or the final budgetary impact. In two cases, a spending ceiling was applied, while in anoth-

According to this study, 3 of the 15 agreements implemented in Catalonia were focused on rare or minority diseases (in gastroenterology, nephrology and respiratory), and all of them were agreements based on economic results

er, a price-volume agreement was used. As a result, the aggregated results of the report do not provide more detailed information on the specific costs.

In any case, it is known that the 15 agreements carried out during the four years of analysis in Catalonia allowed the system to recover almost 2.5 million euros, which is equivalent to 0.21% of the annual hospital pharmaceutical expenditure of Catalonia.

Rare diseases are generally associated with high initial uncertainty regarding their clinical and economic outcomes, especially when real-life evidence is not yet available. However, due to the ethical problem of the lack of alternatives, risk-sharing agreements may be a wise strategy for the agents involved. With this approach, the payer is partially covered by the risk of financing a drug that is less effective than expected, the manufacturer may recover, even partially, its investment in research and development, and the patient is given access to the treatment they need without any delay.

In my opinion, it would be important to apply a top-down financing decision strategy for these diseases that would make it possible to recentralize the catastrophic risk of these pathologies. One approach to consider in the short term is to pay for disease's fees instead of product prices. In the long term, efforts should be made towards paying for the actual health outcomes achieved, with an imperative ex-post evaluation that allows pricing and financing decisions (including divestments) to be made as real evidence becomes available. Risk-sharing agreements based on health outcomes can also be considered as an alternative.

To be able to pay for results, it is essential to measure them properly. Therefore, a key element for the adequate monitoring and evaluation of the results of the joint risk-sharing agreements is the record-keeping, which must be operational, interoperable, and ideally completed automatically without taking up excessive time for healthcare professionals. For example, having a data manager can help with this process.

# IMPLEMENTING OUTCOMES-BASED MANAGED ENTRY AGREEMENTS (OBMEA) FOR RARE DISEASE TREATMENTS: NUSINERSEN AND TISAGENLECLEUCEL


*Karen M. Facey, Jaime Espin, Emma Kent, Angèl Link, Elena Nicod, Aisling O'Leary, Entela Xoxi, Inneke van de Vijver, Anna Zaremba, Tatyana Benisheva, Andrius Vagoras, Sheela Upadhyaya: PharmacoEconomics (2021) 39:1021–1044. https://doi.org/10.1007/s40273-021-01050-5*

**JOSÉ LUIS SEGÚ TOLSA**

*Director-Principal Consultant. PharmaLex*

## SUMMARY

The objective of this research was to review the use and operational implementation of outcomes-based managed entry agreements (OBMEA) in the field of pharmacotherapeutic innovation targeting orphan and ultra-orphan diseases. The analysis was conducted for two cases (nusinersen and tisagenlecleucel) across countries in the European Union, European Economic Area, Australia, New Zealand, and Canada. The authors justify the analysis by the need to explore approaches that facilitate the operational development of this type of agreement.

According to the authors, a significant portion of therapeutic innovations in the field of orphan and ultra-orphan diseases have limited clinical evidence regarding their effectiveness and efficiency. Nevertheless, since these innovations target pathologies with significant unmet needs, regulatory authorities tend to grant conditional commercialization authorization. In such circumstances, outcomes-based managed entry agreements (OBMEAs), whether at the individual level (Payment for Results) or at the population level (Coverage or financing conditioned on evidence development), can help incorporate potentially valuable therapeutics while generating valuable information about their usage.

The two selected cases offer distinctly different therapeutic pers-

pectives (cancer vs. degenerative, potentially chronic vs. one-time treatment, and different target populations).

The methodology used in this study is primarily qualitative. The study utilized a structured questionnaire to obtain relevant information on OBMEAs in various national decision-making contexts. In February 2020, experts (including evaluators, payers, and/or academics) from each of the included countries were asked to complete the questionnaire using publicly available information.

One of the authors reviewed the completed questionnaires and recorded and tabulated the responses. The group of authors of the article held two virtual workshops to discuss the results, analyze differences in the processes across settings, identify new initiatives, and propose potential areas for future collaboration related to OBMEAs for the treatment of rare diseases.

Regarding the results, a significant number of the surveyed settings were not included in the evaluation either because they did not respond, the analyzed products that were not financed at that time, or they were financed without using an OBMEA.

Tables 1, 2, and 3 in the article provide a structured summary of the results obtained for each dimension that was assessed, including the indication financed, the date of the decision, access conditions, population included in the agreement, duration, objectives of the agreement, reassessment conditions included, agents involved in the agreement development process, treatment withdrawal criteria, sources of information, information recorded for monitoring the agreement, frequency of information collection, and the existence of an analysis plan. It is important to note that not all required information is available for every country.

Nusinersen is analysed in three countries (Belgium, England, and the Netherlands, Table 1), where the product is incorporated through Conditional Coverage to the Generation of Evidence (CCGE). Table 2, on the other hand, describes the characteristics of individual OBMEAs (Payment for Results) identified in six countries (Bulgaria, Ireland, Italy, Latvia, Lithuania, and Poland) for the same product. Table 3 presents the results obtained for tisagenlecleucel in six countries. In four of these countries (Australia, Belgium, England, and France), the OBMEA is population-based of the CCGE type, while in the other two countries (Italy and Spain), the OBMEA is individual-based on results.

The first element to highlight is that it was difficult to obtain the information. It was only available after close interaction with experts (co-authors of this article) who knew where to find it on their national websites and could help translate key information.

To summarize, the most remarkable elements of the analysis are the following:

- OBMEAs are typically agreed upon through negotiations between the marketing authorization holder and the payer, although in several countries, physicians and research groups may also be included in the process. Only England and the Netherlands mentioned the participation of patient groups.
- The population and outcomes included in the OBMEAs were based on measurements used in clinical trials.
- The design of the OBMEA, including the clear identification of uncertainties to be resolved and the methods to resolve them (such as sample size, outcome variables, data recording and management processes, sources, and statistical analysis plan), was not clear for all CCGE examples analyzed.
- In very few cases (such as Belgium and England), the OBMEA incorporates the follow-up and evaluation of patients who were not included in the study (as a comparative cohort with control risk adjustment).
- The data that was collected was similar in different countries, but the duration of the agreements differed without clear justification.

**The first element to highlight is that it was difficult to obtain the information. It was only available after close interaction with experts (co-authors of this article) who knew where to find it on their national websites and could help translate key information**

- Not all countries appear to have implemented monitoring processes that ensure compliance with the established protocol and the integrity of the information.

- None of the OBMEAs addressed the regulatory requirements for post-license data and how they could strengthen the evidence in the future and be used in conjunction with the data obtained from the OBMEA itself.

The study has resulted in the development of a checklist that can be used to determine the feasibility of conducting an OBMEA for the treatment of a rare disease.

I would highlight the following conclusions as the most relevant made by the authors:

- OBMEAs are being implemented in different countries to manage uncertainties related to the long-term clinical efficacy of innovative treatments.

- OBMEAs should not become a routine practice, since their implementation is costly for all parties.

- The costs and feasibility of collecting enough data to inform decisions should be considered upfront, and steps should be taken to ensure its quality and integrity.

- It is essential to promote transparency in reporting analysis plans, updates on the status, and results of OBMEAs.

- The information should be publicly available and, perhaps, integrated into a joint database of the different jurisdictions.

- The exchange of information between countries could reduce efforts and enable learning, which is particularly important for the treatment of rare diseases.

- Work is needed to bring the clinical and evaluator/payer communities together and align clinical records with the needs of all parties.

- Evaluators/payers from different countries should collaborate to align their assessments, agree on decision-relevant uncertainties, and define a common data set. This could improve the efficiency of data collection and optimize retesting.

- Post-reimbursement evidence generation should not only aim to resolve uncertainties but also capture new insights into disease and treatment optimization in real life. For this, the involvement of patients and their informal caregivers would seem essential.

**Funding**: This study is part of a project funded by the European Commission (H2020 IMPACT HTA) aimed at developing an appropriate evaluation framework for the treatment of rare diseases.

## COMMENT

The article (Facey K, Espin J et al. 2021) addresses the challenges that affect the incorporation of therapeutic innovation into health systems, focusing the analysis on orphan drugs and the access mechanisms linked to OBMEAs.

Although the article is fundamentally qualitative, it analyzes in-depth two cases and the experiences of OBMEA development in different regulatory environments to obtain useful information to optimize the application of these models.

**It is critical to collect sufficient data from the outset to inform decisions and take steps to ensure its quality and integrity**

Regulatory agencies, such as those in Europe, have fostered the development of innovations aimed at treating orphan and ultra-orphan pathologies and facilitating their incorporation into the market since the 1990s. Methodologies and incentives have been developed to address the low profitability expectations that these products may have for the innovative industry. The objective of these regulatory policies is to ensure that patients with rare and low-prevalence pathologies have access to adequate solutions and, therefore, improve equity of access to effective therapies in the system.

These policies have been successful, and the development of products aimed at orphan and ultra-orphan pathologies has grown exponentially in the last 20 years. However, the problem is that once these products are on the market, conditions must be implemented to make them accessible to patients, including financing the innovation. Public payers are, therefore, faced with the difficulty of articulating access to therapeutic innovation marked by a high price and a level of uncertainty in relation to the value provided, which is often high.

The situation may not seem new, but it is new for both the innovative products and the market that must incorporate them. Traditional financing formulas do not respond to the potential uncertainties (economic or health) of current innovative solutions. Among the potential solutions, Innovative Access Models (IAMs) are identified, such as the OBMEAs discussed in this article, which condition financing on the result obtained, either at the individual level (Payments by Result) or at the population level (Conditional Coverage with Evidence Development) (Vreman et al. 2020, EFPIA 2020).

A recent OECD study (OECD 2019), cited in the article, identifies that 60% of the countries that make up this organization have used IAMs for the incorporation of innovation. The basic objective declared by payers when deciding to use them is to limit the economic impact and respond to the uncertainty in the efficiency of new therapeutic technologies (OECD 2019).

The Spanish NHS is no exception. There are currently more than 21 IAMs active, of which more than 50% are linked to results. The VALTERMED model, even with some deficiencies derived from the registration system, has already produced 4 reports of product results with OBMEA. Our system can certainly be improved, but the rate of incorporation of models linked to results is growing and represents a clear opportunity for improvement if we know how to take advantage of it.

Obtaining information from the applied MAI, especially those linked to results, is not easy. The OECD report already highlights the scarcity or absence of evaluation available due to the confidentiality of the agreements. In addition, the almost non-existent exchange of information between public payers is identified, not only regarding the economic impact but also the evidence generated in relation to uncertainties.

These deficiencies reduce the economies of scale of the OBMEAs and prevent the generation of knowledge and learning, not only in economic aspects but also in those that may be of interest to patients, professionals, and payers, such as the effectiveness of therapies, subpopulations most benefited, management guidelines, or knowledge gained in the management of the disease.

The article provides practical knowledge on how OBMEAs can be more effectively and efficiently utilized, highlighting the importance of their design, the information that needs to be collected and analyzed, and the need to ensure a sufficient population size to draw meaningful conclusions. The authors do not view OBMEAs solely as an economic access mechanism, but rather as a means to obtain relevant data that can improve knowledge, disease management, and facilitate dynamic reassessment of innovation.

They also point out the need to carefully select where these models are applied. As they have a high cost of implementation, the benefits of their use must be clear. The authors also recommend involving patients in the decision-making process and comparatively evaluating the evolution and results of those groups of patients who do not have access to innovation.

**The article provides practical knowledge on how OBMEAs can be more effectively and efficiently utilized, highlighting the importance of their design, the information that needs to be collected and analyzed, and the need to ensure a sufficient population size to draw meaningful conclusions**

At this point, I think it would be appropriate to add to the authors' recommendations the need to anticipate and adapt to changes in the market when designing and applying OBMEAs. For example, nusinersen was the first drug to modify spinal muscular atrophy, but today we already have other commercially available alternatives (such as gene therapy) and some that are close to being commercialized. The pace of innovation incorporation is rapid, and OBMEAs must necessarily anticipate it and even be used to generate comparative knowledge derived from the application of alternative therapies to similar populations and through similar outcome measures.

The authors provide recommendations and propose actions to obtain valuable knowledge about innovation and diseases through the implementation of OBMEAs. They also emphasize the potential of developing a shared innovation

evaluation model among different decision-making bodies, such as the European Union. This could allow for a standardized assessment of innovation, clearly identifying uncertainties, defining the required information for registration, and establishing uniform criteria for patient selection in OBMEAs. In addition, this model could also anticipate changes in the therapeutic landscape and build evaluation models linked to a pathology rather than a specific product, further enhancing its benefits.

If we are not able to establish collaborative frameworks, the value of OBMEAs ends up being limited, mainly focused on attempting to mitigate the uncertainties in the product's price. In the case of ultra-orphan diseases, for a single jurisdiction and taking into account the cost of developing and implementing these models, this is a small reward.

But, in my opinion, there are still aspects that need to be addressed beyond agreeing on evaluation and analysis capacities. Despite the efforts made by regulatory authorities to encourage innovation for orphan and ultra-orphan diseases, effective patient access is still lacking. For example, within the European Union, although there is a single regulatory agency, there are still 27 states with different priorities, capacities, and decision-making mechanisms, resulting in inequitable access. The article itself identifies many countries in the European economic area where the analyzed cases are not financed.

It is not about advocating for universal financing of all therapies, but it is clear that countries have different economic capabilities. For instance, Germany has a GDP per capita that is almost double that of Spain, and

Spain is not the least prosperous country in the EU. Can we expect Spain to have the same ability to adopt innovation as Germany? How can we ensure the equity that the European Union has been striving for since the 1990s?

The European Federation of Pharmaceutical Industries and Associations (EFPIA) has proposed equity-based tiered pricing (EBTP), where drug prices would be determined by a country's ability to pay. However, in my personal opinion, this proposal may not be enough to guarantee equitable access. The prices of these drugs are already very high, and countries with some market capacities are already negotiating discounts (although these are not always made public).

Perhaps it is time to consider whether the concentration of analysis and evaluation capacity should be accompanied, in some cases (such as ultra-orphans), by the establishment of dedicated European funds that can make equity operational in their respective territories. We have already done this with COVID-19. Why not extend the economies of scale that membership in the European Union entails, and ensure that all members have access to effective and necessary innovation (which adds value), while also generating knowledge about its value and the associated pathology?


Vreman RA, Broekhoff TF, Leufkens HG, Mantel-Teeuwisse AK, Goettsch WG. Application of Managed Entry Agreements for Innovative Therapies in Different Settings and Combinations: A Feasibility Analysis. Int J Environ Res Public Health. 2020 Nov 10;17(22):8309.

Addressing Healthcare Challenges - Novel Pricing and Payment Models: New solutions to improve patient access. 2020. Available from: https://efpia.eu/media/554543/novel-pricing-and-payment-models-new-solutions-to-improve-patient-access-300630.pdf.

Performance-based managed entry agreements for new medicines in OECD countries and EU member states: How they work and possible improvements going forward. 2019. Available from: http://www.oecd.org/els/health-systems/health-working-papers.htm.
https://www.sanidad.gob.es/profesionales/farmacia/valtermed/home.htm

# MAKING SURE THAT ORPHAN INCENTIVES TIP THE RIGHT WAY IN EUROPE

*Denis Horgan, Jasmina Koeva-Balabanova, Ettore Capoluongo, Beata Jagielska, Ivana Cattaneo Marta Kozaric, Birute Tumiene, Jean-Paul El Ahl, Jonathan A. Lal, Dipak Kalra y Núria Malats. Helthcare (2022) 10, 1600. doi. org/ 10.3390/healthcare10091600*

**SOLEDAD CABEZÓN RUIZ**

*Cardiologist at the Virgen del Rocío University Hospital*

**SUMMARY**

The article, co-signed by various institutions dedicated to oncology research, personalized medicine, and multinational pharmaceutical companies, aims to justify the importance of maintaining the current regulatory framework for Orphan Medicinal Products (OMPs) research in the European Union (EU). This framework was established in Regulation 142/2000 of the European Commission (EC) and is currently under review. The article argues that altering this framework could jeopardize research in the field of Rare Diseases (RDs) as it may no longer be financially viable for the pharmaceutical industry. The current incentives would be reduced, resulting in a potential lack of return on investment. The Regulation in question has significantly contributed to the approval of new OMPs, increasing from 8 in 2000 to 190 currently. The article highlights that limited accessibility to these medications may stem from regulatory discrepancies and a lack of specific funding availability in different Member States. It suggests that the high costs, risks, and uncertainties associated with research in this field are compensated by the prices of OMPs, which are deemed to be balanced.

Throughout the article, efforts are made to counter the main criticisms of the current regulation and its implementation. It questions proposed modifications under discussion, such as changing the definition or threshold beyond prevalence (e.g., incidence or subgroups of "ultra-rare" diseases), arguing that such changes are unnecessary. The article opposes altering exclusivity to a variable and conditional nature or introducing time limitations to Orphan Drug Designation (ODD), as these measures could undermine the attractiveness of the research

sector in OMPs. It even cites the European Pharmaceutical Strategy, which recognizes the need for new incentives to support research in sectors like this one.

## COMMENT

In 2016, the Council urged the European Commission (EC) to conduct a comprehensive review of the incentive system that specifically targets RDs. The European Parliament also echoed this call in its Report on Measures to Enhance Medicines Accessibility within the European Union (EU).

RD in the EU are defined as those with a prevalence of less than 5 per 10,000 inhabitants. Currently, there are around 7,000 known RDs, with approximately 250 new ones being identified each year. The impact of genetic diagnostic techniques is expected to lead to a possible increase in the number of identified RDs. In Spain, RDs are estimated to affect 3 million people, and between 30 and 40 million people in the EU, which represents more than 6% of the population.

The lack of economic attractiveness for the private sector due to the small number of patients is considered the main cause of insufficient research in ODs. As a result, the USA (1983), Japan (1993), Australia (1997), and the EU (2000) developed a system of incentives for ODs research. Regulation (EC) 141/2000 provides lower requirements in studies, exemption from fees, and ten years of market exclusivity, among other incentives.

Article 1 of Regulation 141/2000 aims to establish a community procedure for the designation of orphan drugs and provide incentives for the research, development, and commercialization of orphan drugs. For the designation of orphan drugs, two paths are established in Article 3(1)(a): the path of the prevalence of the disease ("... [the product] is intended for the diagnosis, prevention, or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10,000 people in the Community when the application is made application…") and the path of return on investment (ROI) ("..and that, without incentives, it is unlikely that commercialization of the drug in the community would generate enough return to justify the necessary investment").

Application 847/2000 of the Regulation specifies a list of all the information necessary to carry out the assessment of 'sufficient profitability' (including data on production and marketing costs, subsidies, and tax incentives). An EC communication (2016/C) indicates that the evaluation will be made "...based on all past and future development costs and expected revenue." However, the inference of the FDA's position was chosen, which suggests that the prevalence threshold is sufficient to assume that research in RES is not profitable.

Of the 2,302 Orphan Drug (ODs) designations granted between 2000 and 2015, the prevalence route was used in 2,301 cases (99.96%) and the ROI route was used in only one case (0.04%).

The first question to ask is whether the regulation has been as effective as expected. Although the EMA has approved more than 2,400 ODs 22 years after the entry into force of Regulation 141/2000, the number

**It would be necessary to have the real costs of investment in research by the industry and what is paid for medicines, about which there is a lack of transparency**

of OMPs authorized annually has remained relatively stable in the last decade, resulting in a total of 190 commercial authorizations of OMPs, which represents around 2.7% of the defined RDs. Of these, only about twenty are new molecules, with curative intent in only 5%, and 40% for oncology. Regarding efficiency, it would be necessary to have transparent data on the real costs of investment in research by the industry and what is paid for medicines, which currently lacks transparency. Some studies point to a lower cost due to lower study requirements. However, surrogate variables, short follow-up periods, absence of comparisons with alternative therapies or subsequent evaluation of the results, despite rapid access to the market, generate limited evidence, which, in part, conditions the entry of drugs into national health systems. For example, algalsidase, a drug approved for Fabry disease, did not show any improvement after a comparison of results between 2000 and 2012.

On the other hand, the lack of evidence in many cases, combined with the high prices of ODs, has led to unequal authorization and public financing by different Member States. In Spain, which funds around 50% of the 190 ODs authorized by the EMA and more than 88% of those authorized in Spain, the drug bill accounts

for 5% of the total healthcare expenditure, with an average annual cost of treatment of 150,000 euros.

And the truth is that, beyond Germany, in most of the EU countries with the highest GDP, despite the important variations in the percentage of medicines authorized by their agencies, the percentage of publicly reimbursed ODs differs greatly from the 190 authorized by the EMA: 58% in Spain and Italy, 57% in France (with 100% financing), 40% in the UK or around 30% in Sweden.

One of the main criticisms leveled at the Regulation is that it has become a fast and highly lucrative business model, leading to a shift in the industry's portfolio towards research in this sector. An example of this is the case of primary bile acid chenodeoxycholic acid (CDCA), which has been used since 1976 for the treatment of gallstones at a price of 0.28 euros per capsule. After being authorized in 2017 for marketing as an ODs for cerebrotendinous xanthomatosis (CTX), where it was already used in an unauthorized manner, its price increased to 140 euros per capsule, which is 500 times the original price. In the case of lenalidomide (Revlimid®), it was authorized in 2018 for a third indication as an orphan drug for multiple myeloma after being authorized, also as an ODs, for certain types of myelodysplastic syndromes and lymphomas. In 2015, lenalidomide was the ninth best-selling drug in the world with 5,800 million dollars. On the other hand, it is worth mentioning the so-called "salami" strategy. With advances in genetics and the typing of cancer by subcategorizing them, such as the definition of 12 types


of lymphomas according to cell type, this strategy has led to an extraordinary increase in the cost of cancer treatment, representing 40% of ODs authorizations.

While it is true that the Regulation has increased the number of ODs since its entry into force, which is satisfying for patients who do not have other options, it is also true that there have been certain dysfunctions throughout its implementation, as pointed out by the EC in its review report. These dysfunctions include the lack of availability and accessibility of ODs, insufficient research in priority areas or areas of greatest therapeutic need, the artificial application of the regulation in common diseases, and technical inefficiencies.

Numerous organizations, Member States, and the EC itself have opened a debate on interesting proposals. It is important to underline the position in favor of Eurordis, the largest association of patients with RDs, which represents more than 960 organizations in 63 different countries, 26 of which are EU Member States. Eurordis points out the necessity and possibility of creating a new ecosystem in which promises of "fair prices," "affordability," "sustainability," and "predictability" can be fulfilled, improving competitiveness and strengthening the European research ecosystem.

Among the proposals are:

- A demand for new incentives is not deemed necessary, but rather for framing and limiting their use. Exclusivity should be limited and variable in terms of time and conditions.
- The impact evaluation must take into account the impact on innovation and also on the accessibility and affordability of medicines. The price and reimbursement policy of the Member States must be reviewed, and the number of indications of the ODs should be considered.
- Innovation must be adequately evaluated in terms of quality, level of evidence, existence or not of alternatives, rare disease severity, and impact on health, as well as orphan drug targets.
- Revision of the definition, including the incidence to the prevalence threshold. The notion

of "rarity" must be evaluated to avoid the "orphanization" of common disorders.

- The identification of unsatisfied needs that allows establishing investment priorities. Eurordis requests a new definition of unmet medical need through proper implementation of Article 3 of Regulation 141/2000, which refers to the life-threatening or chronically debilitating nature of the condition as a requirement for ODD.

- Medicines Law & Policy points out the opportunity to recover the "withdrawal clause," focused on public health, trying to avoid excessively high prices or excessive profits, which would eliminate exclusivity in your case.

- Extension of the application of the flexibilities of the TRIPS, specifically the use of compulsory licenses for ODs.

Perhaps the most innovative proposal among the above mentioned is the "withdrawal clause," which could generate considerable discussion. This proposal focuses on public health and aims to prevent excessively high prices or excessive profits that may eliminate exclusivity in certain cases. The discussion on the meaning of "sufficient" profitability in the context of ODs should be opened, as the justification for incentives is the lack of return on investment.

ML&P proposes to fully implement Article 8(2) of Regulation 141/2000, which defines the line between 'sufficient' and 'excess' profitability and, therefore, between 'sufficient' and 'insufficient' profitability. The Return on Investment (ROI) approach, stipulated in the implementation of Regulation 847/2000, Commission guideline 2008/C82, and Commission Communication 2016/C83, should be used to determine this, and not just the prevalence threshold for ODD through a "give-out clause". It even suggests the possibility of providing a mechanism to "recoup" financial support if an orphan drug turns out to be profitable.

However, after reviewing the main reform proposals for Regulation 141/2000, I must point out what appears to be a missed opportunity by the public sector, as its role could be crucial in terms of effectiveness, efficiency, and equity in this area. Despite significant investment of public resources, often funding research and then paying again for the drugs, it is difficult to understand why a European Public Research Network on ODs is not being promoted as a potentially more effective, efficient, and equitable model.

It is estimated that in Spain, 60% of biomedical research is publicly funded. At the European level, the European Strategy for Rare Diseases promotes and supports the current network of Reference Centers of strategic interest for the registration and investigation of these diseases. In 2019, the Joint European Program on Rare Diseases was approved to bring together resources at the national and European level, including public and non-profit entities, to coordinate access to information on rare diseases and research data. However, there is no information on the exploitation of results or the regulation of the public-private relationship in this regard. Despite the growing public investment in the research of new drugs and the transfer of results to the private sector, accessibility has not improved.

On the other hand, Lamata's evaluation of the Study on the Economic Impact of the Supplementary Protection Certificate and Pharmaceutical Incentives and Rewards in Europe, carried out by the consultancy Copenhagen Economics and commissioned by the EC, indicates that the European pharmaceutical bill, or what it pays the most for, after deducting all the costs of a new medication, is 92,386 million euros.

## CONCLUSIONS

In summary, I share the same concern as the authors of the article regarding the urgent need to find a solution for patients with rare and complex diseases through research. I strongly agree with the need for a comprehensive and open revision of Regulation 141/2000, otherwise it will only lead to more frustration for patients. The current incentive model for the private sector is inefficient in terms of research, economic cost for the public sector, and equity for patients, which poses a real threat to the regulation itself.

The EC's revision proposals must include conditions and obligations for the beneficiaries of incentives and rewards to balance the system fairly and efficiently. Nevertheless, I must emphasize the importance of recognizing the potential and responsibility of the public sector in addressing these diseases by actively engaging in research. It is crucial to consider the substantial amount of public funds already being allocated, both directly and indirectly, to the private sector.

# THE ADDED VALUE OF A EUROPEAN REFERENCE NETWORK ON RARE AND COMPLEX CONNECTIVE TISSUE AND MUSCULOSKELETAL DISEASES: INSIGHTS AFTER THE FIRST 5 YEARS OF THE ERN RECONNET

*Talarico R., Aguilera S., Alexander T., Amoura Z., Andersen J., Arnaud L., Avcin T., Marsal S., Beretta L., Bombardieri S., Bortoluzzi A., Bouillot C., Bulina I., R Burmester G., Cannizzo S., Cavagna L., Chaigne B., Cornet A., Corti P., et. al. Clin Exp Rheumatol (2022) 40 Suppl 134(5):3-11. doi: 10.55563/clinexprheumatol/d2qz38*

**ANTONI MONTSERRAT MOLINER**

*Consultant on public health issues for the European Commission. Member of the National Committee of the Rare Diseases Plan of Luxembourg. Member of the Board of Directors of ALAN-Maladies Rares in Luxembourg and member of the Scientific Committee of FEDER Spain*

## SUMMARY

Five years after the European Commission's approval of the ERNs (European Reference Networks), this article presents the concrete development of one of the 24 ERNs created in 2017, namely the ERN ReCONNECT, which is dedicated to rare and complex musculoskeletal and connective tissue diseases. This group includes various pathologies, such as the Antiphospholipid Syndrome (APS), Ehlers-Danlos Syndrome (EDS), Systemic Lupus Erythematosus (SLE), Idiopathic Inflammatory Myopathies (IIM), IgG4-related diseases (IgG4), Sjöengren's Syndrome (SS), Systemic Sclerosis (SSc), Mixed Connective Tissue Disease (MCTD), and Undifferentiated Connective Tissue Diseases (UCTD).

The ERNs were developed as a result of Directive 2011/24/EU of the European Parliament and the Council of March 9, 2011, which focuses on the application of patients' rights in cross-border healthcare. In agreement with the Member States, the European Commission created 24 ERNs in 2017, with almost 900 highly specialized health service provider centers from 313 hospitals in 26 Member States initially participating. In subsequent calls, up to 620 new applications were incorporated. In the case of ERN

ReCONNECT, 25 service provider centers initially covered the needs of 28,500 patients in eight Member States. After the 2022 call, there are now 55 full-fledged provider members and nine affiliated entities corresponding to 23 Member States, including Spain, participating in the ERN ReCONNECT. It is also important to highlight that the ERN ReCONNECT includes the participation of an ePAG (European Patient Advocacy Group) with the mission of conveying the opinions of patients and collaborating in the development of the ERN. One of the co-spokespersons of this ePAG is Silvia Aguilera (from SAF Spain).

At a global level, ERN ReCONNET is envisioned as an infrastructure that transcends national boundaries, with the aim of providing a platform for health professionals and external stakeholders (such as other networks, authorities, health systems, private actors, etc.) to exchange feedback, experiences, and needs. Additionally, ERN ReCONNET seeks to promote harmonization, strategies, and actions to (i) enhance healthcare standards across the EU, (ii) mitigate inappropriate practices and healthcare disparities, (iii) facilitate transparent decision-making, (iv) improve the translation of research into practice, (v) facilitate efficient resource utilization, (vi) strengthen research and epidemiological surveillance, and (vii) enhance the knowledge of clinicians, healthcare providers, patients and families.

**ERN ReCONNET is conceived as an infrastructure that goes beyond national geographical limits, whose purpose is to serve as a meeting point for needs, feedback and experience for health professionals and the external environment**

In the practical development of these general principles, ERN ReCONNET has focused its activities on various macro areas:

- Clinical Practice Guidelines (CPG): Before planning the development of new CPGs, they carried out an in-depth review of the existing guidelines related to the 10 diseases included in the ERN. The review was compiled in a supplement dedicated to the CPGs and ERN ReCONNET in RMD Open, an official journal of the European Alliance of Rheumatology Associations (EULAR). The review concluded that valid and well-constructed CPGs exist for some diseases, while others have very few or no CPGs. Activity in recent years, and still ongoing, has focused on adapting existing CPGs to different geographic contexts related to four diseases (SS, SLE, IIM, SSc) and is being carried out through the ADAPTE methodology. The goal of this process is to build on existing CPGs to improve the production and efficient use of high-quality tailored guidelines. The tailoring process has been designed to ensure that the final recommendations can address specific health issues relevant to the context in which they are used and address the needs, priorities, legislation, policies and resources in each target setting, which is particularly crucial in CPGs for this group of diseases.

- Patient care pathways (PCPs): A structured methodology was created to enable the design of PCPs based on extensive knowledge sharing on high-quality care and characterized by a strong patient-centered approach, called the RarERN Path™. This methodology aims to improve the organization of care, with integration of the perspectives of large communities of patients, experts, doctors, health economists, hospital managers, and healthcare providers from different EU countries.

- Education: One of the main objectives of ERNs is to exchange and disseminate knowledge about rare and complex conditions. To achieve this, ERNs are specifically requested to organize teaching and training activities on the conditions they cover. ERN ReCONNET experts have shared their expertise in webinars targeted at the network's main audiences. Several webinars were designed specifically for healthcare professionals on the diseases covered by ERN ReCONNET (e.g. EDS, RP, SLE, etc.), while others focused on cross-cutting issues relevant to all diseases covered by ERN ReCONNET (e.g. nutrition and vitamin D). Recently, a survey was conducted to identify the needs of patients and the community of health professionals. The survey results will serve as a starting point for co-designing ERN ReCONNET's education and training strategy for the coming years.

- Clinical patient management system (CPMS): CPMS is an IT

platform developed by the EU to support the diagnosis and treatment of rare diseases by different ERNs. It is complemented by the European Connectivity Facility (CEF) to ease efficient transnational exchange between the contact points (Hubs) defined in various Member States.

- Records: In order to harmonize and ensure data collection across the field of rare diseases, the European Commission launched a call to develop registries within ERNs. ERN ReCONNET is one of the ERNs that received funding for the development of a registry, called Together ReCONNET. The main objectives of this registry infrastructure are to promote a harmonized approach to data collection on the diseases covered by ERN ReCONNET, integrate and implement existing data, and facilitate research. With the creation of the Together ReCONNET infrastructure, knowledge will be generated and the clinical management and care of patients with connective diseases will be improved.

The article concludes that the management of rare diseases continues to represent a great challenge and emphasizes the importance of formal collaborative cross-border networks in this field. The ERN ReCONNET infrastructure is highlighted as a great innovation in the field of rare and complex musculoskeletal and connective tissue diseases, bringing together patients, physicians, and other stakeholders to join forces and collaborate to improve the lives of those affected. In the first five years, the network has successfully built a powerful new infrastructure.

## COMMENT

This article is part of a stocktaking exercise by the vast majority of the ERNs, after the first five years of their implementation. Finding the right rare disease expert and access to care remains a challenge for many of the more than 30 million people living with a rare disease in Europe. Very often, the health professional is located in another country. It is precisely to address these challenges that the EU created the European

**Upon examining the wide range of projects developed by ERN ReCONNECT, it becomes clear that there is a need for professionalization of these networks, and most importantly, their full integration into national health systems**

Reference Networks. ERNs are virtual networks that connect clinicians and researchers across Europe, allowing for the knowledge, rather than the patients, to travel. Knowledge transfer remains the fundamental objective of ERNs and the work of ERN ReCONNECT is perfectly in line with this logic.

The ERN accreditation requires participating centers to serve as a point of research and knowledge, participate in scientific studies, offer treatment to patients from all Member States, and have adequate facilities to do so. This accreditation exists through a national accreditation system only in a minority of the Member States (such as Spain with the CSURs), and in many states, it does not exist, making accreditation through European calls an essential substitute.

**An ERN is a network of healthcare providers that virtually connects doctors and researchers across Europe, so that knowledge travels, not the patient**

Similarly, the voluntary nature of the work carried out by the accredited centers within the ERN or the ePAG generates certain limitations to their activity. As this work is unpaid and must be carried out within the working day that is often densely charged by their own national needs, it can be challenging for these centers to fully engage in the ERN activities. Examining the wide range of projects carried out by ERN ReCONNECT, it is evident that the need for professionalization of these networks and, above all, their full incorporation into national health systems are objectives that, although not addressed in the article, are easily recognizable as medium and long-term goals.

The first years of experience have shown that the RNAs have succeeded in strengthening cross-border collaboration, involving patients in their activities, and sharing the knowledge of experts. However, it also acknowledges that more needs to be done to increase the diseases covered, reduce administrative burden and unequal representation of participating countries, ensure adequate funding, and integrate ERNs into national health systems. The EU4Health program is seen as a commitment to addressing chronic diseases, and there is potential to extend the scope of ERNs to other complex communicable and non-communicable diseases. How can we build on the successes of the ERN model to ensure the best possible care for rare disease patients in a post-pandemic world? Is the ERN model the way forward for service delivery in a stronger European Health Union?

Upon examining the wide range of projects developed by ERN ReCONNECT, it becomes clear that there is a need for professionalization of these networks, and most importantly, their full integration into national health systems

In the Work Program 2022 of the EU4Health Program, there is an included initiative to support the integration of Rare Disease Networks (RDNs) into national healthcare systems. A Joint Action is proposed between the Commission and all 27 Member States, which is quite unusual for Joint Actions. The objective is to establish the necessary measures for effectively integrating RDNs into national healthcare systems. This includes activities to exchange best practices, concrete proposals, and guidelines for better integration. It encompasses various aspects such as patient care pathways, referral procedures, the development of national networks on rare diseases (including capacity building support for Member States and the creation of national networks integrated with ERNs), as well as guidelines for the development of interoperable national teleconsultation tools with ERNs. Additionally, this initiative takes into account the ongoing preparatory work on the creation of the European Health Data Space (EHDS) as outlined in the EU4Health Programme.

The European reference networks are undoubtedly one of the fundamental elements of the future European Health Union, and the contributions of the ERNs in this activity, including the ERN ReCONNECT, are substantial and necessary.

**MARCUS GUARDIAN**

*Chief Operating Officer at EUnetHTA*

# ADVANCES IN HTA PROCESSES AND CHALLENGES IN THE FIELD OF RARE DISEASES AND ORPHAN DRUGS

**My name is Marcus Guardian. I'm in a civil servant of the Dutch Health Care Institute and I am the chief operating manager of the European Network for HTA, which is abbreviated EUnetHTA 21. It's a current service contract that a consortium of European member states has with the European Commission in preparation of the HTA regulation.**

***What are the main objectives of EUnetHTA?***

**MG:** It is a dedicated service contract that is signed between the members of the consortium and the European Commission. The service contract is aimed specifically at the preparation of the regulation, which entails the delivery of a whole set of rules and templates. Thus, it forms the foundation for the workings of a future system at the European level. We are striving to develop proposals for various methodologies and a framework for joint work that is specifically tailored to joint clinical assessment, joint scientific consultations, early assessment, early identification of health technologies, as well as work on the methodological side.

This representation showcases the four subgroups established under the HTA regulation, which serves as the framework we have been developing over the past two years. It is built upon the Joint Action EUnet 3, originally initiated in 2016 and concluded prior to the start of EUnet 21. Therefore, this collaborative framework has a long history that ultimately led to the implementation of the regulation.

***In recent years, there have been notable advances in HTA processes. How do you perceive these advancements, and what impact do they have on decision-making in healthcare?***

**MG:** The benefit of HTA is that it allows for a higher degree of informed decision-making at the national level. So those who must take decisions on reimbursement, those who have to make decisions which new technologies to introduce into healthcare systems get a better overview when HTA reports are used. These reports enable a compari-


son between existing therapies for certain conditions, which would not be possible otherwise. These comparisons are unique and enable decision-makers to make more informed choices. Additionally, in an ideal world, HTA can lead to more realistic and socially transparent prices.

The transition from National HTA to the European Joint approach is quite unique. In the past, each of the 27 member states in the European Union individually assessed the exact same dataset provided by the industry. This process was not only inefficient but also involved a significant duplication of work. It was evident early on that closer collaboration was necessary to address these issues. Beyond the cost aspect, there are additional benefits to working together, such as learning from each other and increasing the overall quality and usability of the assessments across member states. These were the fundamental ideas behind the joint clinical assessments. It's important to note that the system clearly defines the categories in which assessments take place, and the joint clinical assessments focus solely on clinical aspects.

The four clinical domains are examined jointly at the European level. However, the appraisal, cost analysis, cost-effectiveness, and other elements directly or indirectly related to national-level decision-making remain within the jurisdiction of individual member states. This approach combines the joint work, sharing of expertise and knowledge, and increased quality. When looking at the clinical aspects of an assessment, each member state receives the joint report generated from this collaborative effort. They can then utilize these European reports in their national settings, incorporating cost analysis and any additional topics necessary for national reimbursement decisions.

This approach is highly unique, and the anticipation for its implementation in 2025 is quite exciting. A significant amount of preparation has been undertaken in recent years, and the coordination group under the Regulation began its work last year. The relevant subgroups are also taking shape, and EUnetHTA is providing the methodological framework and foundation for these activities. It is a source of pride that all the expected deliverables have been accomplished, and now it is up to the coordination group to determine how to proceed with these achievements.

***What are the main achievements that EUnetHTA has reached since its establishment?***

**MG:** You have very tangible elements. Such as, out of the service contract, we were assigned to provide certain deliverables within a very short time frame. So, we were expected to provide a methodological framework for a system that has far-reaching impact on the future of new medicines in the European market. Within two years, I think that in itself speaks for its success. We have delivered more than 74 deliverables in this very short period. But it's not only the

fact that we delivered them, but also the manner in which we did so. For all the major deliverables, we were able to hold public consultations. These public consultations were very extensive procedures where we received hundreds of pages of comments from patients, healthcare professionals, and industry. All of these comments were included, and that was very important to us.

We designed our work exactly in that manner. So, from day one, everyone - every stakeholder, every partner, every government - knew on which day we would publish our consultation processes and at what time decisions were taken. So, it was a challenge for everyone to be part of this. It was a challenge for our amazing colleagues across Europe who have been working on this to be timely. But that timeliness, that very strict, rigid structure in terms of when we have to provide deliverables, allowed us to be as inclusive and as transparent as we could be with the stakeholders, and that was our main aim. We needed to have the view from our partners, especially the patients, especially the healthcare developers... And it was a huge challenge, and we are quite proud of doing that. And beyond that, I think it has also shown that the collaboration between member states, the collaboration between HTA bodies in Europe, is really strong, and it will hopefully allow us, as a European market, to grow more together and allow more patients in Europe to get access to new medicines. Because with this Joint European Clinical Assessment Report, it will be much easier for developers and industry to use the same report in every member state to launch their product. We hope that will trigger earlier access to new medicines in every European market and for a much broader group of patients in Europe than it has been in the past.

***How do you see the future of HTA processes evolving, particularly in relation to rare diseases and orphan drugs?***

**MG:** There is a fundamental misunderstanding that highly innovative products often come to market with an evidence base that is not necessarily as complete or following the same traditional pathways as the gold standard. Consequently, there is a fear that these products will not receive reimbursement opportunities. The question is whether sticking to the gold standard for evidence generation and assessment automatically excludes innovative products. Additionally, how can we ensure that those who develop these new innovative products consider the evidence needs early on, much earlier than they currently do?

We must also separate the notion that a clinical assessment requires evidence. We cannot assess what is not there, and it is not the responsibility of HTA bodies to bridge that gap. Therefore, if a developer cannot produce evidence, our role is simply to highlight the limited amount of evidence or the lower level of evidence provided compared to more traditional evidence generation methods.

This alone does not automatically lead to a situation where innovative products are not reimbursed. However, it is crucial to ensure that those who negotiate prices are aware of the strength or weakness of the provided evidence. In situations where there is uncertainty and innovative products only offer a weak evidence base, the risk or uncertainty associated with those products must be taken into account. Fortunately, governments and decision-makers are increasingly considering this aspect when making reimbursement decisions.

***From EUnetHTA, what key policy recommendations or initiatives are proposed to help address the challenges in the field of rare diseases and orphan drugs?***

**MG:** One element that we fully support and have been working on for a long time is what we refer to as scientific consultations or scientific advice in the regulatory domain. For almost a decade, we have partnered with the EMA and other regulatory entities to provide such scientific consultations and advice. Through these efforts, we strongly encourage developers, particularly those working on highly innovative products, to seek these scientific consultations as early as possible before finalizing their trial designs. By incorporating these advices and consultations, they can align their trial designs more effectively with the evidence requirements of regulatory bodies.

Based on our experience and expectations, this approach will significantly enhance the value of the generated evidence and, consequently, improve its quality and relevance in later stages. This, in turn, will hopefully facilitate smoother negotiations and greater acceptance for reimbursement of individual products within healthcare systems, provided the evidence is positive.

**SIMONE BOSELLI**

*Public Affairs Director EURORDIS – Rare Diseases Europe*

# THE VOICE OF RARE DISEASE PATIENTS IN EUROPE

***What is EURORDIS?***

**SB:** We are a non-governmental alliance of patient and patient-driven organizations. We have over 950 registered organizations in 73 countries and aim to be the voice for the 30 million people living in Europe who are affected by rare diseases. Our mission is to improve the lives of those living with rare diseases by connecting with patients, empowering them to make decisions that impact their lives, and advocating for better treatment, improved care, and increased social integration at local, national, European, and even global levels. This is our ultimate goal. We have been in operation since 1997. I joined in 2017, and I am about to celebrate my fourth anniversary in a couple of days. I recall that when I first joined, we had around 700 members. In just four years, more than 200 additional associations have joined us. This encapsulates the essence of our work, and we remain dedicated to enhancing the lives of individuals living with rare diseases. Throughout our more than 20 years of work, we have actively supported various legislative, political, and communication initiatives.

***International Rare Disease Day: What would you highlight?***

**SB:** International Rare Disease Day is perhaps the central pillar of our advocacy efforts. We have been globally celebrating this day for over a decade, marking it on the last day of February each year. In my view, this celebration has effectively drawn attention to the multitude of rare diseases we face and underscored the resilience of our community, contributing significantly to the betterment of many people's lives. This year was arguably one of the best, with over 100 countries from around the world participating in numerous events and illuminating national landmarks in support of the cause. As an Italian, it was particularly gratifying for me to witness the iconic Leaning Tower of Pisa adorned in the colors of Rare Disease Day.

***What is your opinion about European policies on rare diseases?***

**SB:** Europe has consistently been at the forefront of action in the field of rare diseases. The Regulation on the Development of Orphan Medicinal Products dates back to 2000 and stands as one of the key recent policy actions. We are

presently working on its update. The primary goal of this project was to create a favorable European environment for research and development of new treatments for rare diseases. The Regulation incorporated a fundamental principle, asserting that individuals living with a rare disease deserve the same quality of treatment as the general population. This principle, in turn, incentivized the development of orphan drugs. While these European policies have regulatory aspects, they also aim to enhance the access and funding processes through various orphan drug designation programs and accessibility to additional forms of support, such as scientific and legal advice, and market exclusivity.

Since 2000, we have designated over 200 therapies as orphan drugs. This could be perceived as a success. Nonetheless, it's now an opportune moment to assess what has been effective and what hasn't. Some aspects have not improved, as they aren't solely dependent on regulation. In particular, certain areas require even greater incentivization, like ultra-rare diseases that haven't witnessed the same level of research and scientific development as others. It's also essential to evaluate what has been successful and strive for improvements wherever possible, particularly in enhancing accessibility to treatments.

An illustrative example can be found in Spain. Given its regionally based healthcare system, disparities and inequalities exist among the different Autonomous Communities. This issue is not present in Italy, but it does persist in Europe, where we observe substantial imbalances in access to centrally authorized treatments. This challenge has been a continuous focus of our advocacy efforts. Specifically, we need a broader and more agile approach to accessing these treatments at the European level, benefitting all Europeans living with physical limitations.

***What do you think was the impact of COVID-19 on Rare Diseases?***

**SB:** COVID-19 has had a significant impact on the rare disease community. Since the beginning of the pandemic, we have addressed this challenge effectively, aligning our activities with the new circumstances. Our longstanding digital working platform allowed our organization to adapt well to the reality of COVID-19. Regarding the well-being of our community, we conducted a barometer survey to precisely understand the impact. The initial survey has already been completed, and the results were presented in November last year. Eighty-four percent of people living with a rare disease experienced disruptions in the care they received. Nearly nine out of ten encountered difficulties in accessing necessary care. Sixty-four percent expressed concerns about their health, and 30% believed that this situation might jeopardize their lives, either probably or definitely. Sixty percent were unable to access diagnostic tests, preventing them from receiving therapies. Additionally, in 60% of cases, surgeries were postponed or canceled. I believe that the impact of COVID-19 will extend beyond the immediate effects of the pandemic.

We have also witnessed some positive developments, particularly the increased use and enhanced relationship with telemedicine and virtual consultations. In the realm of rare diseases, we heavily rely on virtual consultations through the European Reference Networks. We understand that knowledge and expertise for treating specific diseases may not be available in every country, so sharing it virtually has always been our ally in the rare disease community.

***EURORDIS in Spain: How does it work?***

**SB:** EURORDIS has an office in Barcelona. For us, and especially for me, it truly serves as the hub for building patient communities. Our colleagues in Barcelona primarily focus on fostering strong communities and promoting patient engagement and empowerment. We don't expect patients to know how to treat themselves, but we do encourage them to engage in meaningful dialogues with regulators, decision-makers, and clinicians on an equal footing, enabling them to participate in all decisions concerning their health. This is our mission: to assist patients in managing their diseases and enhancing their quality of life. In this regard, the Barcelona office plays a central role in this aspect of our work, offering services such as the academy, summer school, and more.

***What do you see as the main challenges for the future from Europe's perspective?***

**SB:** We are living in a peculiar time, which presents both a challenge and an opportunity for bolstering healthcare systems and investing in health. It is a moment for all nations, Spain included, to contribute to the betterment of Europe. Different countries may not have equal capabilities or readiness to address all recognized rare diseases. Consequently, collaborating at the European level would yield added value at the national, regional, and local levels. This is particularly pertinent for Spain. Therefore, working at the European level will exert a direct impact on the health of all Spanish citizens, not only those living with rare diseases.

## EUROPEAN COMMITTEE URGES EU TO ENHANCE COOPERATION FOR RARE DISEASE CARE

In a recent conference in Bilbao, the European Economic and Social Committee (EESC) has urged the European Union to implement a European action plan aimed at strengthening collaboration between national health systems. The primary goal is to provide improved diagnoses, treatment, and care for patients with rare diseases, which affect over 7,000 conditions and approximately 36 million people in the EU. These conditions are often chronic, disabling, or life-threatening, with up to 95% lacking specific treatments.

The EESC emphasizes that no single EU Member State can effectively address the complexities of rare diseases alone and highlights the importance of the 24 European Reference Networks (ERNs) established in 2017 for knowledge sharing and research. The EESC has been advocating for a comprehensive EU approach since 2009 and recently reiterated the need for EU-wide solutions.

The conference featured high-level speakers and the participation of prominent EU figures. They stressed the urgency of a European strategy to address rare diseases, emphasizing the need for a pan-European solution


to provide optimal care for individuals regardless of their location within the European Union. This action plan is seen as crucial in improving the lives of those affected by rare diseases in Europe.

More information: *https://www.eesc.europa.eu/en/news-media/press-releases/rarediseases-eu-needs-strategy-help-36-million-people-europe*

## OXFORD-HARRINGTON RARE DISEASE CENTRE ACCELERATES RARE DISEASE TREATMENTS

The University of Oxford and the Harrington Discovery Institute at University Hospitals in Cleveland, Ohio have jointly announced the establishment of the Oxford-Harrington Rare Disease Centre Therapeutics Accelerator. This significant development was marked by an official signing event at the University of Oxford, where leaders from both institutions, along with key figures from University Hospitals and Oxford Science Enterprises, were in attendance.

The Oxford-Harrington Rare Disease Centre (OHC) was formed in 2019 as a collaborative partnership between the University of Oxford and Harrington Discovery Institute. This initiative aims to leverage the combined strengths of both institutions to address rare genetic diseases, particularly in the areas of rare neurological diseases, cancers, and developmental diseases.

The Accelerator is a pioneering transatlantic effort designed to identify and support promising academic discoveries that can lead to new treatments for rare diseases. Over the next decade, it seeks to facilitate the development of 40 potential life-changing therapies for rare diseases and secure approvals from regulatory authorities in key markets like the U.S., the U.K., and Europe.

Former U.K. Prime Minister David Cameron, who has a personal connection to rare diseases through his son, Ivan, will lead international efforts for the Accelerator in

his role as Chair of the Oxford-Harrington Rare Disease Centre Advisory Board.

The Accelerator will adopt a unique non-profit/for-profit model, with plans to allocate up to £200 million for new projects. This funding will be complemented by expertise in research, drug development, commercial strategy, and business development from industry leaders experienced in bringing new drugs to market.

The first investment made by the Accelerator in September 2023 led to the creation of AlveoGene, a U.K. company dedicated to developing innovative inhaled gene therapies for rare respiratory diseases.

To support these efforts, the partners are establishing a Rare Disease Impact Fund, which will facilitate investments in projects aligned with the mission of accelerating rare disease therapeutics.

The Oxford-Harrington Rare Disease Centre is working towards transforming the landscape of rare disease treatment and providing hope to patients and their families worldwide through innovative research and collaboration.

More information: *https://www.oxfordharrington.org/*

## ACCELERATING RARE DISEASE THERAPIES: THE ROLE OF THE FDA'S INNOVATIVE PILOT PROGRAM

On September 29th, the U.S. Food and Drug Administration (FDA) initiated a program aimed at expediting the development of novel drug and biological products for rare diseases. This program, known as the Support for Clinical Trials Advancing Rare Disease Therapeutics (START) Pilot Program, offers selected sponsors of products in clinical trials more frequent and direct communication with FDA staff to address specific development issues. This communication can include topics like clinical study design, control group selection, and patient population choices.

The program is available to sponsors with products under an active Investigational New Drug application (IND) regulated by the FDA's Center for Biologics Evaluation and Research (CBER) and/or the Center for Drug Evaluation and Research (CDER). However, eligibility criteria differ between CBER and CDER-regulated products. For CBER, the product must be a gene or cellular therapy addressing an unmet medical need for a rare disease or serious condition likely to lead to significant disability or death within the first decade of life. CDER-regulated products must target rare neurodegenerative conditions, including rare genetic metabolic types.

FDA U.S. FOOD & DRUG ADMINISTRATION

Applications for the START program will be accepted from January 2, 2024, to March 1, 2024, and pilot participants will be chosen based on their readiness to move their development program towards a marketing application. The FDA plans to select up to three participants for each center, and depending on the pilot's evaluation and feedback, a second iteration may be considered.

The FDA is also actively seeking feedback from stakeholders to improve the development of cellular and gene therapies for rare diseases, with plans for meetings, workshops, educational programs, and discussion papers. The agency is committed to providing guidance and regulatory tools to expedite the availability of therapies for rare diseases and will continue to enhance its recommendations for sponsors of rare disease products.

More information: *https://www.fda.gov/news-events/press-announcements/fda-launches-pilot-program-help-further-accelerate-development-rare-disease-therapies*

# Observatory

## ORPHAN DRUGS

CROSS-COUNTRY COMPARISON OF AVAILABILITY OF OD, BY YEAR OF APPROVAL

21

2022 1

CROSS-COUNTRY COMPARISON OF ACCESS TO OD, BY AVAILABILITY RATES

37%

2022 2

CROSS-COUNTRY COMPARISON OF AVAILABILITY OF NON-ONCOLOGICAL OD, BY YEAR OF APPROVAL

15

2022 3

CROSS-COUNTRY COMPARISON OF ACCESS TO NON-ONCOLOGICAL OD, BY AVAILABILITY RATES

35%

2022 4

## TIMELINE

CROSS-COUNTRY COMPARISON OF AVERAGE TIME BETWEEN EUROPEAN MARKETING AUTHORISATION AND NATIONAL APPROVAL (DAYS)

636

2022 5

CROSS-COUNTRY COMPARISON OF AVERAGE TIME BETWEEN EUROPEAN MARKETING AUTHORISATION AND NATIONAL APPROVAL OF NON-ONCOLOGICAL OD (DAYS)

587

2022 6

This observatory compiles some of the main relevant indicators in the field of rare diseases, grouped in six areas.

By clicking on the ⊕ symbol you can observe the evolution over time of some of them.

The symbol allows you to access the source of data origin.

Abbreviations:
RDs: Rare Diseases
OMPs: Orphan Medicinal Products
EMA: European Medicines Agency

### SOURCE OF DATA ORIGIN

1 2 3 4 5 IQVIA

# newsRARE

Scientific dissemination magazine on Rare Diseases

## FOLLOW US ON SOCIAL MEDIA!

This magazine can be downloaded in .PDF format from: www.newsrare.es

follow us on:

**twitter:** @revistanewsRARE

**instagram:** https://www.instagram.com/revistanewsrare/

**facebook:** https://www.facebook.com/revistanewsrare/

PARTNERSHIPS