PROJECT FINEERR



# STRATEGIC REFLECTION ON FUNDING AND ACCESS TO RARE DISEASE THERAPIES IN SPAIN

Fundación Weber

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# STRATEGIC REFLECTION ON FUNDING AND ACCESS TO RARE DISEASE THERAPIES IN SPAIN

March 2022

Report by:

weber

In collaboration with:

Roche

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Edit
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28014, Madrid

Editorial coordination:
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ISBN: 978-84-122101-6-3
D.L.: M-1994-2022
DOI: https://doi.org/10.37666/I13-2022

Madrid, March 2022

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# FOREWORD

Today there are more than 7,000 diseases classified as rare due to their low incidence and prevalence, although the number will continue to grow as scientific advances are able to identify the causes of nosological entities that, as of today, lack a characterisation as a disease. However, in aggregate, these RDs affect around three million people in our country, which makes them a major health problem, both in terms of population size and impact on individuals. This daily suffering in its different facets, physical, psychological and social, must drive the actions of organisations to face this enormous challenge, because by remedying the problem of individuals we will be able to solve the problem of societies.

In recent years, advances in diagnostic technologies, their implementation in the NHS and the adaptation of regulations to a clinical reality differentiated towards RDs have made possible to draw a path that, being difficult and tortuous, should give us hope. Specifically, the Instituto de Salud Carlos III (ISCIII) launched the IMPACT infrastructure aimed at resolving, with all the scientific power of the country, the unfinished diagnoses of so many people who, after the evaluation with all the available healthcare technology, still remain without a diagnosis. This infrastructure, designed by Dr. Raquel Yotti during her time as director of ISCIII, is the continuation of the different actions that the ISCIII has historically put in place in this area since the creation of an ISCIII centre expressly oriented towards this type of disease: the RDs Research Institute, with various transversal programmes, such as the RDs Patient Registry or the Undiagnosed Cases Programme, to give two examples. Similarly, the ISCIII's alliance with FEDER has resulted in actions of high scientific value for people and families affected by this type of diseases.

However, we are aware that there is still a long way to go before individuals and families affected by RDs can have access to adequate, comprehensive, timely and independent diagnosis, treatment and rehabilitation regardless of their starting conditions. The resolution of the obstacles on this path must derive from a coordinated effort that incorporates the perception and experience of the people affected, but also the general interest represented in a bidirectional and loyal interaction between the other agents involved in their health care.

The FINEERR project brings together many of the actors, with the aim of reflecting on the different paths that can be taken to provide the best possible care for people affected by RDs and their families. The work introduced in this document provides interesting data that give us an idea of the current situation, and the discussion about it outlines the different areas where progress needs to be made. I therefore invite those who read this document to reflect on these data, as it will be the calm and daring debate that will allow us to promote the construction of solutions to the problems raised. In this sense, the recent approval by the Council of Ministers of the Strategic Project for Economic Recovery and Transformation in Vanguard Health should be understood as an opportunity to make progress in this field as well as in others because its impact on people will encompass broad areas of knowledge aimed at anticipating and solving people's problems. In short, the Government's

actions, in combination with the initiatives arising from people-centred reflection, will provide the set of actions on which we will advance to improve our NHS through Science. This project and the document included here are a clear example of the path towards reflection.

**Dr. Cristóbal Belda Iniesta**
Director of the Instituto de Salud Carlos III

Rare diseases (RDs), often of genetic origin, affect small to ultra-small populations of patients. Most RDs are chronic, progressive, degenerative, disabling and frequently life-threatening. Each of the over 6,000 identified RDs affects a very small population, but altogether they affect 25 to 30 million of people in Europe, or the population of Belgium and the Netherlands combined. And this is without taking into including carers, families and friends [i].

The European framework for incentives in orphan medicinal products has provided some successes, with 6.3 million people potentially benefitting from the Regulation, over 200 authorised dedicated products placed on the European market, increase in research activities including clinical trials and stimulated both public and private investments. However, it has also focused development on disease areas where treatments already exist, not equally focused on adults and children, and benefitting  a few disease areas concentrated on the 'least rare'.

Our evidence tells us we need to work on two major axis. On the one hand, more treatments and therapies are needed. Two thirds of people living with a RDs reported having received treatments directly linked to their RDs. Those treatments are mainly symptomatic: only 6% have experienced a curative treatment while 42% had symptomatic treatments, 25% have had a treatment that aimed to slow down or stop their disease and 4% received a treatment that aimed to prevent the disease. Another third reported having never received a treatment directly linked to their RDs. The main reason being that, according to them, there are no existing treatments. On the other hand, people with RDs often cannot get the treatments they needed because it is not available where they live, or because the treatments they needed because the waiting list was too long, or because the treatments are not affordable or cannot travel to other countries because they do not have the financial support needed.

In today's world, science and technology offer an unprecedented chance to address the unmet medical needs of people living with a RDs. This potential is currently not translated into actual health benefits for the large majority of people living with a RDs due to issues concerning availability, accessibility and affordability of treatments. In our 2018 paper 'Breaking the Access Deadlock to Leave No-One Behind', we already identified the top three issues that we see having the most impact on access to innovative therapies for people with RDs:

1) **An economic model that fuels mistrust between payers and companies:** due to their complexity, orphan medicines pose many different challenges to competent national authorities for pricing and reimbursement, not least as they increasingly tend to arrive to at marketing authorisation with higher levels of uncertainty on efficacy and effectiveness.

2) **A vast disconnection between the value of a product and the price claimed:** we see real life cases of new products for diseases with high unmet medical needs being approved for commercialisation by regulatory authorities but never making it to the patients who need them most because they are deemed too expensive or not seen as presenting sufficient value for national healthcare systems.

3) **The cost of developing new therapies remains too high,** despite advancements in modelling and assessment techniques that could decrease investments dramatically.

i Wakap SN, Lambert DM, Olry A, Rodwell C, Gueydan C, Lanneau V, et al. Estimating cumulative point prevalence of RDs: analysis of the Orphanet database. Eur J Hum Genet.(2020);28(2):165-73.

# PREFACE: THE EURORDIS VISION

The remarkable technological and scientific advances of the past years unlocked the potential of diagnostic tools for RDs and present an exponential increase in novel technologies and therapies on the market. These new opportunities embody hope for patients, but in parallel bring about concerns in terms of safety, long term efficacy, access and of sustainability for health budgets.

The ten recommendations of the FINEER Project are clearly synergic and complementary with what we see as way forward to an improved ecosystem for RDs R&D in Europe, for example:

- Ensure that patient perspective is taken into account in the research, development but also regulatory, assessment and appraisal processes.
- Develop the conditions for an agile drug manufacturing capacity to withstand critical situation such as drug shortages, market withdrawal and expiry of patents.
- Reinforce the EU centralised processes of the Regulations for special populations in a structured and seamless way for all RDs therapies.
- Address the challenges related to patient access to Advanced Therapeutic Medicinal Products (ATMPs), and the robustness of the relevant regulatory framework.
- Ensure legal clarity to facilitate access to treatment across borders to approved treatments;
- Develop a common European methodology to set a fair price based on a transparent, dynamic, mutually constructed approach to match R&D with unmet needs and healthcare priorities.
- Strengthen European cooperation in pricing and negotiations by setting a 'European Table of Negotiations' to negotiate and procure therapies, supported by risk sharing incentives such as a fund to support data generation post-MA.

The RDs community aspires to a research, development and delivery ecosystem for RDs therapies in Europe in which efforts at the local, regional, national and international levels remain concerted for success. In line with the Rare 2030 Foresight Study recommendations [ii], streamlined regulatory, pricing and reimbursement policies should be fostered.

These policies should encourage a continuum of evidence generation along the full life cycle of a product or technology as well as the patient journey from diagnosis to treatment access. These policies can contribute to develop a European ecosystem able to attract investment in areas of unmet need, foster innovation, and address the challenges of healthcare system sustainability.

This ecosystem must be co-designed by both public and private sectors. The COVID-19 crisis showed us the necessity of collaboration at international level, including regulatory cooperation, in order to maximise resources and to adapt to new ways of developing medicines and delivering care to patients with the help of remote and digital tools. Coordinated, more strategic policies are required to address these shortcomings and inequalities and ultimately improve the health outcomes and quality of life of people living with a RDs.

**Simone Boselli**
Public Affairs Director
EURORDIS - Rare Diseases Europe

ii : Kole, A., Hedley V., et al. (2021) Recommendations from the Rare 2030 Foresight Study: The future of RDs starts today.

One of the main conclusions I reach from my experience in the field of RDs is that we cannot predict the future, but there is one thing we can do: prepare for it and consequently create it, in a way. FINEERR presents itself as a valuable tool to anticipate this future, learning from past experiences and achievements.

Looking back a little more than two decades ago, RDs were virtually unknown. However, from then until now, we have **begun to make visible the story of those who live with them**. This is the story of those who have waited and still wait for years to name the disease, the story of uncertainty facing the lack of information, the story of those who put all their hope in research for a cure or treatment, and the story of those who, even though they have medicines, are having difficulties to its access.

A story that we began to write thanks to the birth of the associative movement on RDs, in 1997, when the European Alliance for RDs (EURORDIS) was born, the first reference entity that brought together more than 30 million people who, it is estimated, live with these pathologies on a continental level. Two years later, in 1999, the Spanish Federation for RDs (FEDER) was born; in 2013, the Ibero-American Alliance for RDs (ALIBER) and, in 2015, the International RDs Network (RDI).

The consequences of these first steps became tangible in the visibility of the collective, but also in the implementation of the first legislative framework focused on RDs in Europe, with the impulse of Regulation (EC) Nº 141/2000 of the European Parliament and of the Council of 16 December 1999 on ODs, which marked a turning point in our cause.

Under a regulatory framework that was created to encourage research on RDs, more than 168 ODs have been designated since 2000 to date. This is a clear example of how international efforts contribute to improving the approach to RDs.

In other words, on our path, we have learned that despite the heterogeneity of our cause, unity is our best asset to face the common problems we encounter from the local to the global. But also that, if all the stakeholders involvedworked as a network, we could really transform our reality.

**The FINEERR project** was born in this context, in which I have had the pleasure of representing people with RDs in this strategic and joint reflection on the funding and access to therapies for RDs in Spain.

This project is also an example of bringing together the experience and perspective of more than 40 experts, while integrating patient representatives, which is precisely one of the demands of the movement and one of the main recommendations we extract from the project, legitimising their participation.

Regulation (EC) Nº 141/200, in addition to being a turning point in the recognition of patients' rights and the incentive to research, also set a precedent by establishing what would become the Committee for Orphan Medicinal Products (COMP) of the European Medicines Agency and even integrating patient representation along with the rest of the experts. We need to give continuity to this benchmark, guaranteeing and legislating the real participation of patients at all levels and in processes such as the Therapeutic Positioning Reports. This call for the incorporation of patients for cooperation between all agents is one of the recommendations and measures included in the FINEERR decalogue.

Among the measures considered most relevant by our expert group, the **digitalization of networks and access to international databases comes first**. In other words, ensuring interoperability between national and European data. In this regard, it is worth noting that more than 95% of people with RDs or in search of a diagnosis are willing to share their data to improve healthcare and to promote research. However, 80% require full or almost full control of their data, as their greatest fear is that the information will be shared with third parties without their consent (50%) or that the information will be used in different contexts (47%).

In addition, achieving patient management of their own data and cooperation between health systems across borders will prevent patients from having to explain their medical records over and over again each time they see a new doctor. Yet even today, incompatible formats and standards continue to be used in electronic health record systems across the European Union, although the current pandemic provides a direct demonstration of how data will transform health and healthcare.

Sharing data on RDs at the European level will allow to enlarge the sample of patients and overcome geographical dispersion, as well as to broaden knowledge and extrapolate it between countries. It would also avoid duplication and reduce time and investment in research, making an impact on diagnosis and treatment.

In the case of diagnosis, in addition to the challenges shared with all the countries of the world due precisely to this lack of information, in Spain the idiosyncrasy of our NHS is added, as is reflected in the second measure that has received the most support: **harmonising diagnostic procedures between the different Autonomous Communities**.

In Spain, almost 30% of families with RDs or in search of a diagnosis have been forced to travel outside their province to name the disease or access treatment, in search of expertise that is often concentrated in large hospitals.

In the face of this, it is essential to work towards comprehensive health care that guarantees referrals to Reference Centres, Services and Units (CSUR) and to continue to promote, more than ever, that the knowledge travels, inside and ouside of our country through the European Reference Networks.

Furthermore, in order to improve this situation, it is necessary to address the heterogeneity of the neonatal screening tests performed in our country, as they vary between 7 and 40 depending on the place of residence. In addition, neonatal screening should be understood as the gateway to the first treatment.

About the treatment, which is the third most supported measure of the project, it is referred to **the importance of data collection for medicines for RDs**, highlighting the need for direct information from patients, as well as the direct and indirect costs and the impact of these medicines for the patient and the patient's family.

However, despite the willingness of patients, many citizens in Europe currently have limited electronic access to data about their own health. In Spain, within the State Register, patients are represented through FEDER which is part of the Working Group developing the RDs State Register (ReeR) Manual of Procedures. However, a European framework could make the ReeR information accessible to patients anonymously and safely and ensure that it serves RDs research.

All the above while the European Data Space is being created and the frameworks that affect these measures the most are being revised: Regulation (EC) Nº 141/2000 itself and Directive 2011/24/EU of the European Parliament

and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare; in addition to the revision of Spanish Royal Decree 1015/2009 of 19 June, which regulates the availability of medicines in special situations.

In short, everything we have discussed throughout the development of this project is a new opportunity for **a future we cannot predict, but we can build**. A future focused on achieving Universal Health Coverage and the 2030 Agenda, in which people, regardless of where they live and the disease they live with, can access timely and with equity to the diagnosis and treatment.

**Thanks to all the people who have promoted and participated in this project**, on behalf of the 3 million people who live with a RDs in Spain, those who are waiting to receive a diagnosis and all the reference organisations. Thank you for making this possible and for being there for the families.

**Alba Ancochea**
Director
Spanish Federation for Rare Diseases (FEDER)

# LIST OF ABBREVIATIONS

| | |
|---|---|
| AACC | Autonomous Communities |
| AEMPS | Spanish Agency for Medicines and Health Products *(Agencia Española de Medicamentos y Productos Sanitarios)* |
| AIFA | Italian Medicines Agency *(Agencia Italiana de Medicamentos)* |
| ASMR | Amélioration Du Service Médical Rendu - Relative Improvement of the Therapeutic Benefit |
| CFT | Pharmacotherapeutic Commission *(Comisión Farmacoterapéutica)* |
| CHMP | Committee for Medicinal Products for Human Use |
| CIBERER | Centre for Biomedical Research Network on Rare Diseases *(Centro de Investigación Biomédica en Red de Enfermedades Raras)* |
| CN | National Code *(Código Nacional)* |
| COMP | Committee for Orphan Medicinal Products |
| COVID-19 | Coronavirus SARS-CoV-2 disease |
| CREER | State Reference Centre for Rare Diseases *(Centro de Referencia Estatal de Enfermedades Raras)* |
| CSUR | Reference Centres, Services and Units *(Centros, Servicios y Unidades de Referencia)* |
| CTs | Clinical trials |
| DGCBSSNSF | Directorate General for the Basic Portfolio of Services of the National Health System and Pharmacy |
| DGCSF | Directorate General for the Common Portfolio of Services of the National Health System and Pharmacy |
| EASP | Andalusian School of Public Health |
| EMA | European Medicines Agency |
| ERN | European Reference Networks |
| EU | European Union |
| EUPATI | European Patients' Academy |
| EURORDIS | European Organisation for Rare Diseases |
| FDA | United States Food and Drug Administration |
| FEDER | Spanish Federation for Rare Diseases |
| FINEERR | Strategic reflection on funding and access to targeted therapies for rare diseases in Spain |
| FundAME | Spinal Muscular Atrophy Foundation |
| HTA | Health Technology Assessment |
| ICAM | Madrid Law Society *(Ilustre Colegio de Abogados de Madrid)* |
| ICER | Incremental Cost-Effectiveness Ratio |
| IMSERSO | Institute for the Elderly and Social Services |
| INGEMM-IdiPAZ | Institute of Medical and Molecular Genetics |
| TPR | Therapeutic Positioning Report *(Informe de Posicionamiento Terapéutico)* |
| ISCIII | Institute for Research on Rare Diseases of the Instituto de Salud Carlos III |
| MAPER | Rare Disease Resource Map |
| MCDA | Multi-Criteria Decision Analysis |
| NHS | National Health System |
| NICE | National Institute for Health and Clinical Excellence |
| ODs | Orphan Drugs |
| ONT | National Transplant Organisation |
| PGE | General State Budget *(Presupuestos Generales del Estado)* |
| PP | People's Party *(Partido Popular)* |
| PREM | Patient-Reported Experience Measure |
| PROM | Patient-Reported Outcome Measure |
| PSOE | Spanish Socialist Workers' Party *(Partido Socialista Obrero Español)* |
| QALY | Quality Adjusted Life Years |
| R&D | Research and Development |
| RD | Royal Decree |
| RDs | Rare Diseases |
| SEFH | Spanish Society of Hospital Pharmacy |
| SERGAS | Galician Health Service |
| SESPA | Health Service of the Principality of Asturias |
| SMEs | Small and medium-sized enterprises |
| SMR | Service Médical Rendu - Therapeutic benefit of the medicinal product |
| SpainRDR | Spanish Network of Rare Disease Registries for Research |
| VALTERMED | Information System to determine the Therapeutic Value in Real Clinical Practice of Medicines with a High Health and Economic Impact on the NHS |
| WGs | Working Groups |
| WHO | World Health Organisation |

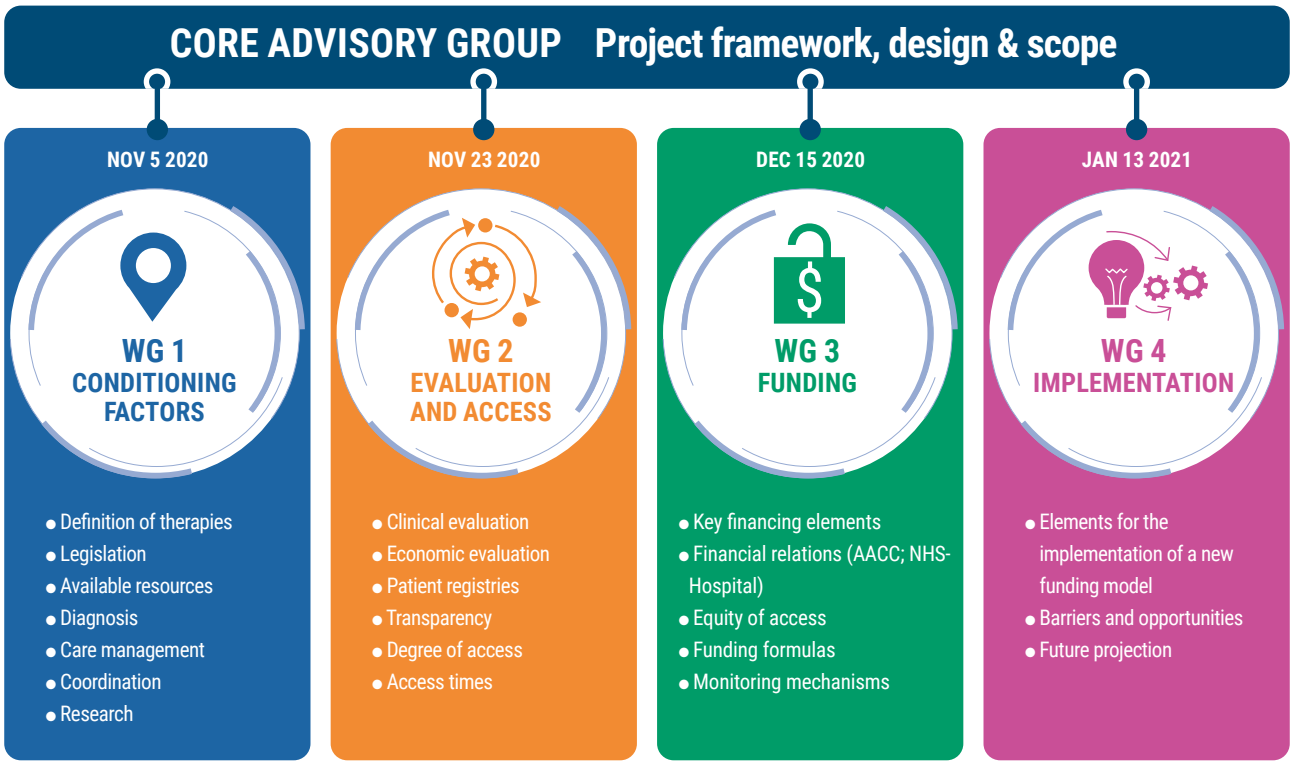
The main objective of the FINEERR project is to carry out a multidisciplinary strategic reflection on the challenge of funding and access to therapies for RDs in Spain. Specifically, it aims to pool the knowledge of 40 experts to reach a consensus on specific proposals for improvement in the medium term, which will help decision-making on the optimal allocation of resources for RDs in the NHS.

This think-tank on funding and access to therapies for rare diseases (RDs) was structured around a CORE Advisory Group and four thematic, multidisciplinary Working Groups (WGs), where experiences and opinions were shared on different relevant aspects of funding and access to these therapies, in order to obtain reflections and recommendations for improvement.

The CORE Group, made up of 7 experts, was responsible for proposing the most appropriate framework, design and scope of the project, and has served as an essential guide throughout the project, validating the strategies, reviewing all the materials sent by the consultancy firm Weber to the WGs, and participating in the meetings of the different WGs.

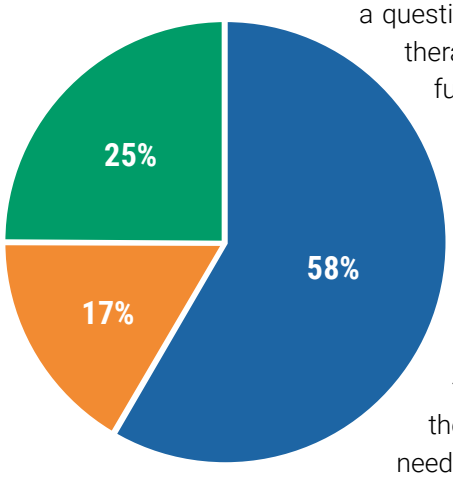
**FINEERR PROJECT DESIGN: WORKING GROUPS AND DATES OF THE SESSIONS**

The first WG addressed the "funding and access conditioning factors" of RD therapies, proposing actions and recommendations around the regulatory framework, clinical conditioning factors and RD research. The second WG was focused on the elements



of "evaluation and access", articulating the discussion and recommendations around clinical evaluation, economic evaluation and timing of the funding process. The third group reflected on the "funding" of therapies for RDs in Spain, making contributions and recommendations on the formulas and key elements of financing and monitoring mechanisms. Finally, the fourth WG, with a more institutional profile, focused on the "implementation" and viability of the proposals made by the other groups, and on the bases for carrying out a new model of financing and access to therapies for RDs in Spain, including additional recommendations.

**CURRENT TIMING OF PRICING AND FUNDING DECISIONS FOR RD THERAPIES IN SPAIN (N=24)**




Prior to the meetings of the WGs, the experts were asked to complete a questionnaire to diagnose the initial situation for these therapies. 73% of respondents considered that the funding and access situation for RD therapies in Spain could be improved, while 23% believed that the situation could be very much improved. In turn, more than half of the experts (53%) thought that the degree of access in Spain is similar to that of neighbouring countries, while 35% believed it was lower. With regard to the timing of pricing and financing decisions for these therapies, 58% expressed the opinion that they are too long, with significant bottlenecks that need to be resolved, while 17% found that they are reasonable, given the casuistry of these therapies.

The WGs collected 50 action measures that could be grouped into 9 thematic areas. In order to rank the different actions, the experts were asked to rank them on the basis of their relevance and, in a second round, on the basis of their perceived feasibility (for the 25 most relevant actions, taken as recommendations).

The most relevant measure (with a relevance average score of 8.59 out of 10) was the digitalization of networks and access to international databases, followed by the specific collection of data for ODs (8.53) and the diagnostic harmonisation between AACC (8.47). The most feasible measures included promoting greater communication between health professionals and patients (97.5%), the mandatory publication of the therapeutic positioning report (TPR) which is already incorporated in the Ministry's new consolidation plan) and a more rapid recruitment of patients for clinical trials.

Four out of the 10 most relevant recommendations were also among the 10 most feasible ones, so special emphasis should be placed on them. These were: mandatory publication of TPRs; improved referral processes for patients with RDs within and outside the CSUR; improved governance of follow-up mechanisms; and the improved communication between health professionals and patients.

**THE 25 RECOMMENDATIONS (MEASURES OF HIGHEST RELEVANCE), RANKED BY FEASIBILITY**

- **2.** Enhance RD research
- **5.** Rapid recruitment for CTs
- **6.** Public-private collaboration in research
- **8.** Diagnostic harmonisation between AACC
- **9.** Improve referral processes within and outside CSUR
- **10.** Improve concessions/funding of the CSUR
- **11.** Increased incorporation of CSUR into European networks
- **13.** Standardised rules of socio-health care
- **16.** National political agreement
- **19.** Specific access procedure to RD-targeted therapies
- **27.** Dynamic clinical and economic reassessment
- **28.** Methodology and deadlines for evaluation and access
- **29.** Mandatory TPR publication
- **31.** More transparency in pricing
- **32.** Greater patient representation/participation in decisions
- **33.** Digital platform for national consultation
- **34.** Validation of specific PROM/PREM scales
- **35.** Better professional-patient communication
- **40.** Systematic application of funding mechanisms
- **41.** Alternative funding models
- **45.** Governance of monitoring mechanisms
- **46.** National registry of RDs
- **48.** Specific data collection for ODs
- **49.** Creation of data manager
- **50.** Digitalization of networks and access to international databases




In conclusion, based on the reflections and recommendations arised from the FINEERR project, it is possible to extract a decalogue of final considerations, which brings together many of the points that were taken into account when the experts addressed changes in the financing and access to therapies for RDs in Spain.

**FINEERR PROJECT DECALOGUE**

1. Differentiation between the different RDs, with focus on those with higher unmet needs
2. More empowered and participatory patients in decision-making processes
3. Comprehensive health care in all areas surrounding the patient: social, family, educational, clinical and pharmacological
4. More powerful, collaborative and attractive R&D in rare diseases
5. More agile and transparent decision-making process
6. Harmonization of diagnostic, referral, assistance and socio-health care processes and access to treatments, for the sake of territorial equity
7. Value-focused differential evaluation, taking into account ethical and humanistic criteria
8. Uncertainty-conditioned financing, through financing mechanisms that allow risk sharing
9. Digitization and dynamic reassessment of innovations, highlighting the importance of a good data collection and its proper use
10. More than good intentions, with greater leadership, governance and coordination

1

# CONTEXT, RATIONALE, OBJECTIVES

In the last 20 years important advances have been developed in the field of rare diseases (RDs), with an increase in awareness of these pathologies, their recognition as a health priority, the approval of specific legislation, improvements in their diagnosis, an increase in scientific activity, the development of new therapies and the creation of a community that includes patients and gives them a voice[1].

The specific regulation of orphan drugs (ODs) has been very positive for the development of new treatments. Between 2000 and 2020, more than 2,300 drugs were designated as ODs in Europe, and the European Medicines Agency (EMA) granted marketing authorisation for more than 190 ODs[2,3]. It should be noted, however, that not all medicines indicated for a RDs need to have an orphan designation, or to have been approved as an orphan medicinal product by the EMA.

Despite progress, there are still significant challenges in funding and access to treatment. Of the more than 3 million people suffering from a RD in our country, 47% do not have access to accurate treatment or consider that the treatment they are receiving is not adequate[4]. Moreover, patients only have publicly funded access to slightly less than half of the EMA-authorised ODs, with a time to reimbursement decision that can take more than 2 years[5].

Therefore, there is a need to reflect on the challenges in financing and access to therapies for RDs in Spain, in order to reduce the gap between the development and use of the drug, increase equity in access to available therapies and, at the same time, introduce coherent, efficient and sustainable strategies in the long term.

*The main objective of the FINEERR project is to carry out a multidisciplinary strategic reflection on the challenge of funding and access to therapies for RDs in Spain from the perspective of the Public Administrations and the NHS. Specifically, it aims to pool the knowledge of 40 experts in order to reach a consensus on specific proposals for improvement in the medium term, which will help decision-making on the optimal allocation of resources for RDs in the NHS.*

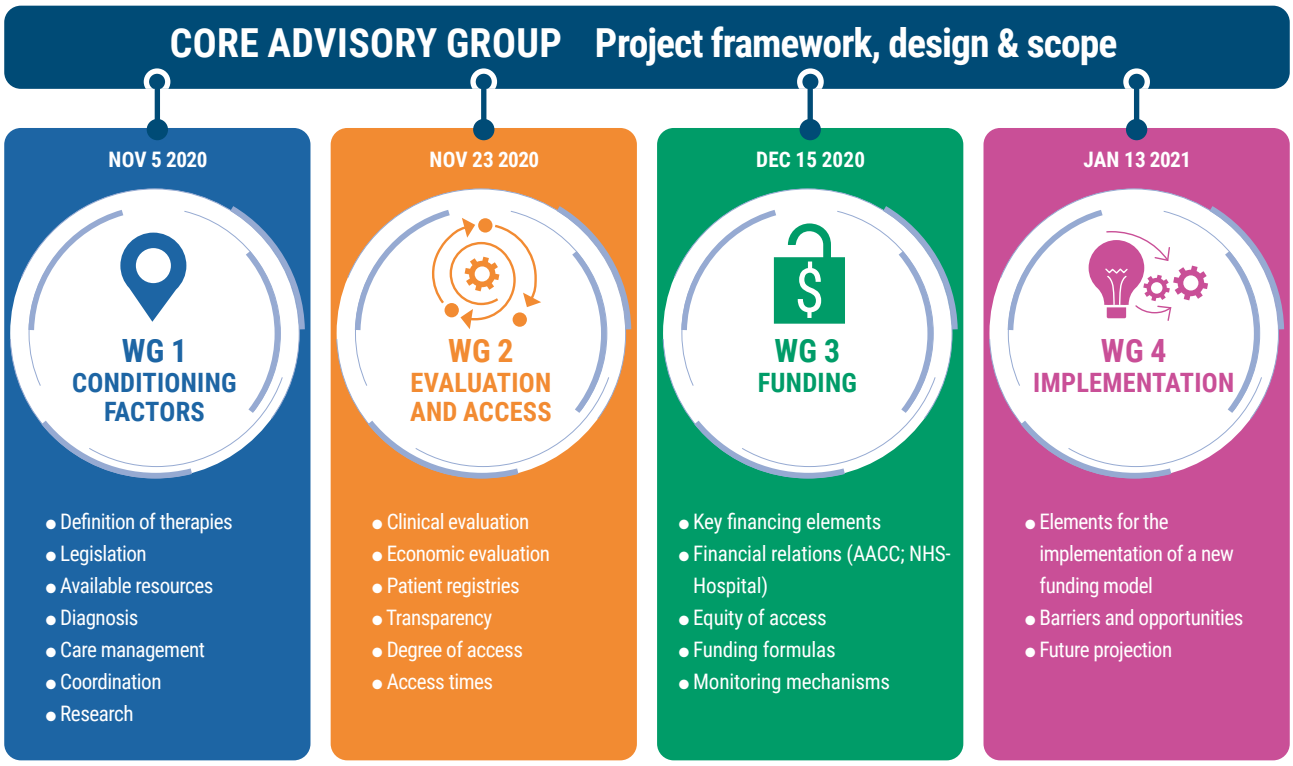
This report is structured as follows. After outlining its methodology, it presents a literature review on key aspects of financing and access to medicines for RDs. The fourth section contains the assessment on the current situation made by the experts who participated in FINEERR.The fifth section brings together the 50 main recommendations for action proposed throughout the project. The report closes with a section of conclusions and final considerations.

# 2

# PROJECT METHODOLOGY

The FINEERR project, led and coordinated by the consultancy firm Weber and funded by Roche, has been implemented through a CORE Advisory Committee and four thematic working groups (WGs), where relevant topics were discussed and agreed upon, such as the conditioning factors, the evaluation and access to therapies for RDs, their financing and the implementation of a new funding and access model (Figure 1).

**FIGURE 1. DESIGN OF THE FINEERR PROJECT: WORKING GROUPS AND DATES OF THE SESSIONS**



## CORE ADVISORY GROUP

The CORE Advisory Group involved 7 experts, who are top-level representatives of the regulatory, institutional, scientific, clinical, economic, managerial, patient and clinical fields (Figure 2). They had an end to end key role throughout the FINEERR project.

At the time of its conception, the CORE Group was responsible for setting out the most appropriate framework and scope of the project. It validated its design and structure, as well as the main topics to be addressed in each of the thematic groups. It also defined the most appropriate profiles for the different WGs, and proposed which experts would be invited to participate.

Throughout the different phases of the project, the CORE Group has dynamically advised Weber, corroborating the steps and strategies to be followed, validating the materials to be sent to the WG experts and reviewing their contents in depth. It was also closely involved in the four thematic meetings as at least one CORE member participated in each group, thus contributing to the global vision of the project.

**FIGURE 2. COMPOSITION OF THE CORE ADVISORY GROUP**






The methodological approach of the WG was as follows. Each group met in an online session, led by Weber. Prior to each meeting, the CORE group validated an online diagnostic questionnaire (different for each WG), which was sent to the experts in the WGs, and which served as an initial assessment of the current situation.

On the basis of this reflection and the pre-reading material prepared by Weber from a literature review (documents previously validated also by the CORE Group), the four working meetings were organised as forums for multidisciplinary debate and reflection. One part of each session was planned for the experts to think and deliberate some recommendations for action in small WGs of 3-4 people. They were encouraged to be creative but also concrete. In the last part of each session, these recommendations were shared in order to clarify, complete and validate them with the group.

Following the four meetings, a list of the 50 main recommendations for action was drawn up and grouped into nine thematic areas. The CORE and WG1-3 experts were then asked to indicate the relevance of each measures through an online questionnaire. Once their responses had been analysed, a new questionnaire was sent to the project experts to rank, according to their feasibility of implementation in the NHS, the 25 measures that that resulted the most relevant in the previously.




## WORKING GROUP 1: FINANCING AND ACCESS CONDITIONING FACTORS

The objective of WG 1 was to discuss and draw out a series of detailed recommendations regarding the **initial conditions for funding and access to therapies for RDs in Spain**. Although the experts were free to make recommendations on all the issues they considered relevant, the discussion of this WG was articulated around the following three main areas and their capacity to improve funding and access to therapies:

- Regulatory framework
- Clinical conditions
- RD research

The multidisciplinary committee included 9 experts from the clinical, economic, legal and research fields, as well as a representative of the CORE Group (Table 1).

**TABLE 1. COMPOSITION OF WORKING GROUP 1**

**WG 1**

| NAME | POSITION |
|---|---|
| **Aitor Aparicio García** | Managing Director of the State Reference Centre for RDs (CREER) under the IMSERSO. Burgos |
| **Antonia Campolongo Perillo** | Nurse, Movement Disorders Unit, Neurology Service, Hospital Sant Pau. Barce-lona |
| **Emili Esteve Salà** | Director of the Technical Department of Farmaindustria |
| **Atanasio García Pineda** | Director General Prestacions i Farmàcia. Conselleria Salut i Consum. Govern Illes Balears |
| **Pablo Lapunzina Badia** | Head of the INGEMM-IdiPAZ Research Group. La Paz University Hospital. Ma-drid |
| **Álvaro Lavandeira Hermoso** | President of the Institute for Health Research and Training. Pharmaceutical Law Advisor at the Madrid Law Society (ICAM) |
| **Alfons Macaya Ruiz** | Head of Paediatric Neurology Section at Vall d'Hebron University Hospital. Bar-celona |
| **José María Millán Salvador** | Researcher at the Instituto de Investigación Sanitaria IIS La Fe. Valencia |
| **Manuel Posada de la Paz*** | Director of the Institute for Research in RDs of the Carlos III Health Institute (ISCIII). OPIS Research Professor in RDs |
| **Ignacio Málaga Diéguez** | President of the Spanish Society of Paediatric Neurology (SENEP)<br>Head of the Neuropaediatrics Unit at the Central University Hospital of Asturias.<br>*Member of the CORE Group of FINEERR* |

**Note:** *MP's participation in this discussion group is in his personal capacity and as Professor of Research in Epidemiology of RDs and in no way representing or acting on behalf of the ISCIII.




## WORKING GROUP 2: EVALUATION AND ACCESS

The objective of WG 2 was to discuss and draw out detailed recommendations regarding the **evaluation and access to therapies for RDs** focused on three broad areas:

- Clinical assessment
- Economic evaluation
- Access

The multidisciplinary committee included 9 experts from the fields of care, economics and management, as well as a representative of the CORE Group (Table 2).

**TABLE 2. COMPOSITION OF WORKING GROUP 2**

**WG 2**

| NAME | POSITION |
|---|---|
| Reyes Abad Sazatornil | Head of Pharmacy, Miguel Servet University Hospital. Zaragoza |
| Jorge Camarero Jiménez | Vice President of PAREXEL Consulting. Former AEMPS scientific evaluator |
| Francisco Dolz Sinisterra | Manager of the Hospital Universitario Dr. Peset. Valencia |
| Víctor Jiménez Yuste | Head of the Haematology and Haemotherapy Department, Hospital Universitario La Paz. Madrid |
| Mencía de Lemus Belmonte | President of the Spinal Muscular Atrophy Foundation (FundAME) |
| Isabel Martín Herranz | Head of the Pharmacy Service of the University Hospital Complex. A Coruña |
| Jorge Matías-Guíu | Director of the Institute of Neurosciences. Head of the Neurology Department, Hospital Clínico San Carlos. Madrid |
| Jorge Mestre Ferrándiz | Independent economic consultant. Associate Professor at the Carlos III University. Madrid |
| Irene Beatriz Zschaeck | Neuropsychologist, Hospital Sant Joan de Déu. Barcelona |
| Marta Trapero Bertran | Professor and researcher at the Universitat Internacional de Catalunya. Barcelona *Member of the CORE Group of FINEERR* |




## WORKING GROUP 3: FINANCING

The objective of WG 3 was to draw out a series of detailed recommendations regarding **the financing of therapies for RDs in Spain**. To this end, the discussion was organised around the following three main areas:

- Key elements of funding
- Financing formulas
- Monitoring mechanisms

The multidisciplinary committee included 7 experts from the academic , business and management fields, as well as a representative of the CORE Group (Table 3).

**TABLE 3. COMPOSITION OF WORKING GROUP 3**

**WG 3**

| NAME | POSITION |
|---|---|
| **José Javier Castrodeza Sanz** | Professor of Preventive Medicine and Public Health at the University of Valladolid |
| **Carlos García Collado** | Deputy Director General for Pharmacy and Services in the Andalusian Health Service |
| **Pedro Gómez Pajuelo** | Ex-Secretary General of the ONT and ex-Deputy Director General of Pharmacy |
| **Caridad Pontes García** | Medicines Manager of the Catalan Health Service |
| **Santiago de la Riva Compadre** | Vice President of the Spanish Federation for RDs (FEDER) |
| **Pedro Luis Sánchez García** | Director of Farmaindustria's Research Department |
| **Luis Verde Remeseiro** | Manager of the Integrated Health Area of A Coruña SERGAS. Academic Director of the Master in Healthcare and Hospital Management at IFFE Business School |
| **Olga Delgado Sánchez** | President of the Spanish Society of Hospital Pharmacy (SEFH). Head of the Pharmacy Service of the Son Espases Hospital. Palma de Mallorca<br>*Member of the CORE Group of FINEERR* |




## WORKING GROUP 4: IMPLEMENTATION

The meeting of WG4 was held after the meetings of the other three WG, in order to learn about and discuss the proposals made by the rest. Then, they could **reflect on their viability and on the implementation** of a new model for financing and access to therapies for RDs in Spain. It should also be underlined that the members of this WG also made recommendations on funding and access that had not been formulated before.

WG 4 included 8 experts from the political, economic and management fields, as well as two representatives of the CORE Group (Table 4).

**TABLE 4. COMPOSITION OF WORKING GROUP 4**

**WG 4**

| NAME | POSITION |
|---|---|
| Soledad Cabezón Ruiz | Former MEP for the PSOE. Cardiologist |
| José Martínez Olmos | Professor Andalusian School of Public Health (EASP) |
| Antoni Montserrat Moliner | Member of the Board of Directors of Alan - Maladies Rares Luxemburgo |
| Rubén Moreno Palanques | Senator for the PP. Member of the Health and Consumer Affairs Committee |
| Ana Pastor Julián | Member of the Spanish Parliament for the PP. Member of the Health and Consumer Affairs Committee. Second Vice-President of the Congress of Deputies |
| Ana Prieto Nieto | Member of the Spanish Parliament for the PSOE. Spokesperson on the Health and Consumer Affairs Committee. First Secretary of the Home Affairs Committee |
| Julio Sánchez Fierro | Lawyer and Doctor of Health Sciences |
| Juan Luis Steegmann Olmedillas | Member of the Spanish Parliament for VOX. Spokesperson in the Health and Consumer Affairs Commission |
| Alba Ancochea Díaz | Director of the Spanish Federation for RDs (FEDER). Member of the International RDs Research Consortium<br>*Member of the CORE Group of FINEERR* |
| Ignacio Málaga Diéguez | President of the Spanish Society of Paediatric Neurology (SENEP)<br>Head of the Neuropaediatrics Unit at the Central University Hospital of Asturias<br>*Member of the CORE Group of FINEERR* |

Therefore, the FINEERR project has involved RDs experts from different fields, such as clinical, care, economic, legal, academic, managerial, political and research ones. Patients were represented in all groups, including the CORE one, as key actors in the system on which the measures are articulated.

The entities where the project participants work range from hospitals to universities, consultancies, professional associations, health services, scientific societies and patient associations (Table 5).

**TABLE 5. ENTITIES PARTICIPATING IN THE FINEERR PROJECT**

| |
|---|
| ALAN - Maladies Rares Luxemburgo |
| Integrated Health Area of A Coruña SERGAS |
| State Reference Centre for RDs, CREER |
| A Coruña University Hospital Complex |
| Conselleria Salut i Consum. Govern Illes Balears |
| International RDs Research Consortium |
| Andalusian School of Public Health (EASP) |
| Farmaindustria |
| Spanish Federation for RDs (FEDER) |
| Spinal Muscular Atrophy Foundation (FundAME) |
| San Carlos Clinical Hospital |
| Sant Joan de Déu Hospital in Barcelona |
| Sant Pau Hospital |
| Dr. Peset University Hospital |
| Hospital Universitario la Paz |
| Miguel Servet University Hospital |
| Son Espases University Hospital |
| Vall d'Hebron University Hospital |
| University and Polytechnic Hospital La Fe |
| La Paz University Hospital |
| Madrid Law Society |
| Institute of Neurosciences |
| Neuropaediatrics Health Service of the Principality of Asturias (SESPA) |
| PAREXEL Consulting |
| Andalusian Health Service |
| Catalan Health Service |
| Spanish Society of Hospital Pharmacy (SEFH) |
| Spanish Society of Paediatric Neurology |
| Carlos III University |
| University of Valladolid |
| International University of Catalonia |

# 3

# RELEVANT ASPECTS FOR FUNDING AND ACCESS OF RD-TARGETED THERAPIES

When tackling such a complex issue, it is essential to review the main relevant aspects to the financing and access to therapies for RDs, some of which will be specific and others common to the rest of the pathologies and therapies. To this end, a non-exhaustive review of the literature has been carried out, which is presented in separate blocks to give the reader an overview of the issues addressed throughout the project, as well as past, present and future highlights.

## 3.1. DEFINITION OF RARE DISEASES

In addition to their low prevalence, RDs are pathologies with particular characteristics, often differing from other common diseases. Many of them start in childhood and are chronic and degenerative, life-threatening and with a high impact on the quality of life of the patient and their caregivers. Because of their particularities, the research and development of therapies to prevent, identify and treat these pathologies is often associated with an unpredictable return on investment and high uncertainty about their clinical effectiveness, which makes them expensive. To mitigate these difficulties, many countries have put in place regulations and specific measures to encourage their development and access.

The first step in implementing specific incentives for RDs is to narrow down their definition. However, there is no single definition of what constitutes a RD[6,7]. Some countries define them according to their relative prevalence, which in turn also varies depending on the country's population. For example, the US considers a RDs when it affects fewer than 200,000 patients in the country, while in Japan when affects fewer than 50,000 patients in the country, and this number drops to 2,000 patients in Australia.

In Europe, as in Australia, a disease is considered rare when it affects less than 1 in 2,000 inhabitants, while the WHO suggests a lower ratio of 1 in 1,000-1,500 affected people. These figures are related to the size of the different countries, with prevalence rates varying between 1 and 8 per 10,000 inhabitants[6].

**PREVALENCE OF A RARE DISEASE**

**USA:** if less than 200,000 inhabitants in the country are affected (ratio of 6.1/10,000)

**Japan:** if it affects less than 50,000 inhabitants in the country (ratio of 4.0/10,000)

**Australia:** if less than 2,000 inhabitants in the country are affected (ratio of 0.8/10,000)

**Europe:** if it affects less than 5 out of 10,000 inhabitants

**WHO:** ratio of between 6.5 and 10 per 10,000 persons

**UK:** ultra-rare if occurring in less than 1,000 people (< 1/50,000)[8]

### 3.2. GENERAL REGULATORY FRAMEWORK: INCENTIVES AT EUROPEAN LEVEL

Since 2000, the European Commission approved a specific regulation to promote therapies for RDs through the Regulation Nº 141/2000[9] and the Regulation Nº. 1901/2006[10] .



Currently, the EMA designates as orphan medicinal product (a medicinal product for a RDs) those therapies that meet the following criteria[11]:

- Target a disease whose prevalence in the EU does not exceed 5 per 10,000 population, or where commercialisation is unlikely to generate sufficient returns to justify the investment required for its development.
- To be intended to be destined for the treatment, prevention or diagnosis of a life-threatening or chronically debilitating disease.
- If there is no satisfactory diagnosis method, prevention or treatment of the condition or, if the method exists, the medicinal product already evaluated presents a significant additional benefit.

In order to encourage the development of therapies designated as orphan, the EMA provides the following benefits[12]:

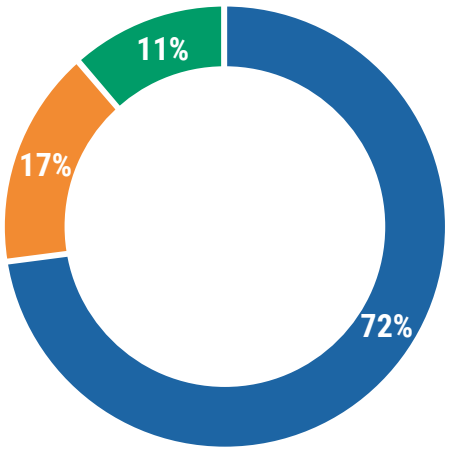
- Centralised marketing assessment, allowing a single decision for all EU Member States.
- Protection from competitors for 10 years. The period of market exclusivity can be extended by 2 years for paediatric medicines.

- Specific scientific advice at a reduced cost, to facilitate a final marketing approval.
- Additional administrative assistance for SMEs.
- Reduction of marketing application fees and annual fees.
- Additional funding for R&D in RDs.

Being designated or not as an orphan medicinal product has no relevance in the marketing authorisation process, as the decisions of the EMA's Committee for Medicinal Products for Human Use (CHMP) on the benefit/risk ratio are made independently of this condition. In this sense, the CHMP acts the same as with other medicines, with no different criteria for authorisation beyond the necessary considerations based on the rarity of the disease[13].

**FIGURE 3. TYPE OF PROCEDURE APPLIED TO EXISTING ODs APPROVED IN 2002- 2020**

**Source:** own elaboration based on EMA[3]

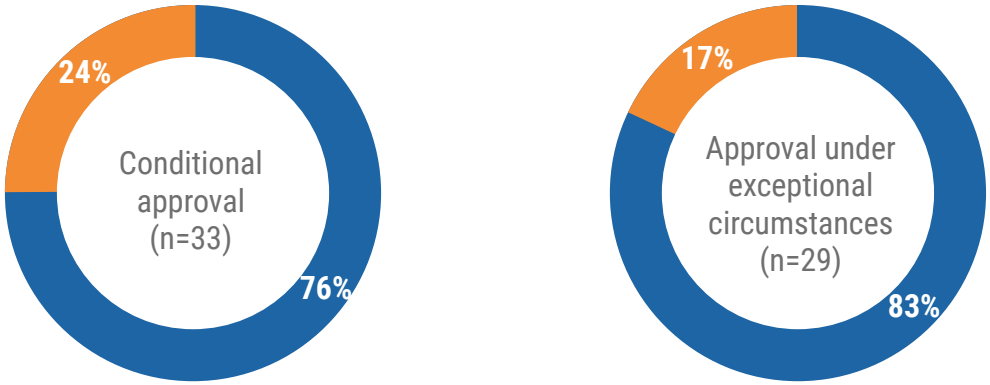



However, for pathologies with no alternative or high mortality risk, the EMA offers some flexibility in the standard clinical evaluation processes, through conditional authorisation and authorisation under exceptional circumstances, used to authorise drugs early and on the basis of less evidence. In practice, of the 116 ODs authorised by the EMA in 2002-2020, 20 (17%) have been approved under conditional authorisation and 13 (11%) under exceptional circumstances, while the remainder have followed a standard procedure (Figure 3)[3].

These exceptional procedures are also intensively used in targeted therapies for RDs. Sixty-one percent of the 33 therapies currently subject to conditional approval and 45% of the 29 therapies approved under exceptional circumstances are ODs. If we broaden the spectrum to RD-targeted therapies (whether or not they have been approved as ODs), this proportion rises to 76% and 83%, respectively (Figure 4).

**FIGURE 4. APPLICABILITY OF EMA PROCEDURES, BY TYPE OF DISEASE, 2002-2020**

**Source:** own elaboration based on EMA [3]



Recently, the European Commission has assessed the effects of the European legislation on access to ODs, indicating that between 6% and 18% of the ODs authorised, since the implementation of the regulation until 2017, could have been a direct result of this legislation[10]. In this context, other authors estimate that up to 55% of authorised ODs are a consequence of the change in legislation[14]. In addition, the European Commission suggests that the regulation has reduced the average time for an orphan drug to enter the market by 9 months, although it acknowledges that the period between designation and authorisation is still too long (10-15 years)[10].

It also highlights other outstanding challenges, such as under-exploited therapeutic areas, which match less profitable ones; unequal access between different EU countries, for commercial reasons of the industry and national pricing and financing policies; and questions the incentive of market exclusivity, since for some RDs the market is starting to be similar to that of conventional medicines.

Therefore, we are in a time for evaluation and review of incentives at European level, including the very definition of a RDs. To this end, the European Commission has launched a public consultation aimed at informing and gathering opinions on its vision of the problem and the possible solutions proposed, which is expected to be formalised in the first quarter of 2022[15].

## 3.3. CLINICAL CONDITIONS

### Diagnosis

In recent years, novel diagnostic methods have been incorporated that have optimised the process and it is expected that in the future, massive genetic sequencing technologies will further promote progress in this field. Despite the advances, delay is a differentiating factor in RDs compared to other diseases. In Spain, it is estimated that the average time to diagnosis of a RDs is 5 years, and the 19% is delayed by 10 years or more (Figure 5).

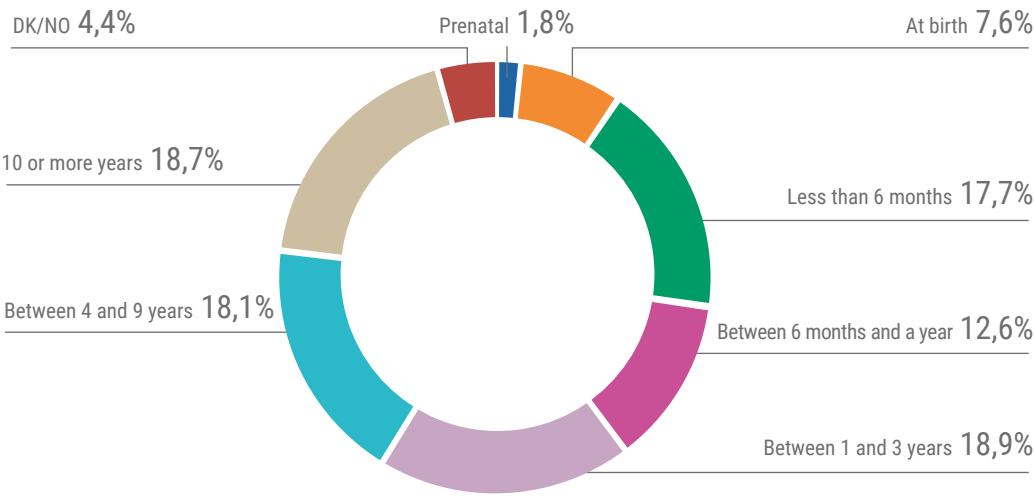



**FIGURE 5. DISTRIBUTION OF PATIENTS WITH RDs IN SPAIN, ACCORDING TO THE TIME OF DIAGNOSIS OF THEIR DISEASE**

**Source:** adapted from FEDER (2018)[4]

In some cases, the problem is the lack of proper diagnosis. It is estimated that 7.6% of patients with a RDs have a non-definitive diagnosis and another 3.2% have no diagnosis[4]. Lack of knowledge about the disease is the main cause of diagnostic problems[4] and causes serious physiological, psychological and emotional consequences for the patients[4]. On the other hand, an accurate diagnosis brings benefits to patients, including improved prognosis, reduced isolation and better social and health care, among others[16].

The smaller the population of the Autonomous Community (AACC) of origin of the patient is[17], the most delayed the RD diagnoses appears to be. In turn, there is an inverse correlation between a longer diagnostic time and patients' knowledge of the Reference Centres, Services and Units (CSUR) for their pathology.

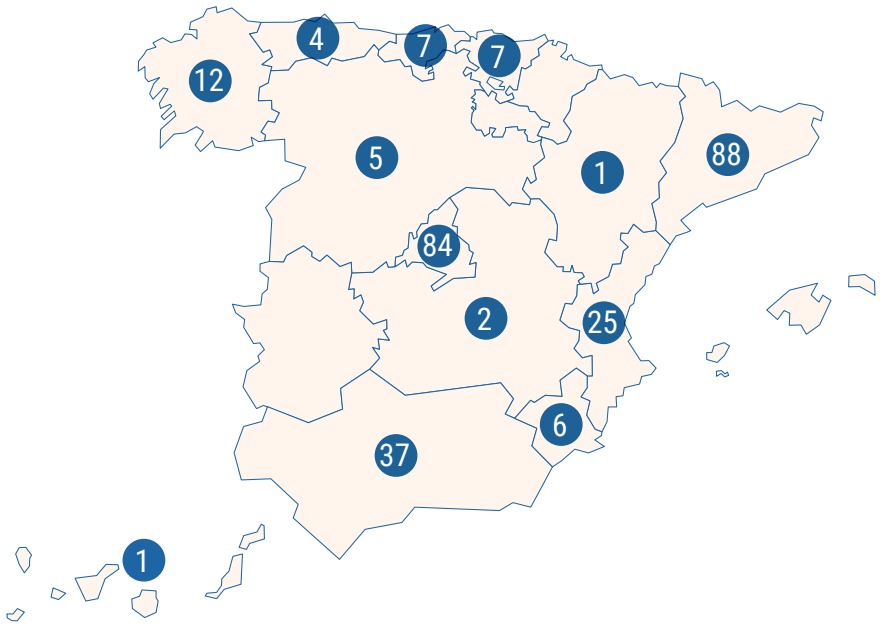
## Care management

Another fundamental element for access to RD therapies is the appropriate care management of patients, which requires a care network that covers all the necessary social and healthcare processes. In Spain, the CSURs are the backbone of the care of people with RDs[18]. In any case, the existence of a centre specialised in a rare pathology does not imply that the continuous care of the patient is carried out there, but rather that it should act as a support for diagnostic confirmation and the definition of therapeutic and follow-up strategies, as well as a consultant for the clinical units that usually care for this group.

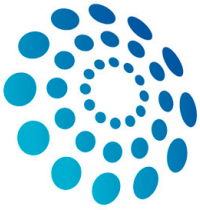
In Spain, there are 279 CSUR linked to more than 70 different pathologies (many of them RDs), spread over 13 of the 17 AACC. Catalonia and the Community of Madrid have nearly the 60% of the CSUR in Spain (Figure 6)[19]. This distribution may increase unequal access[17].

**FIGURE 6. DISTRIBUTION OF CSUR BY AUTONOMOUS COMMUNITY, 2020**

**Source:** own elaboration based on Ministry of Health, Consumption and Social Welfare (2020)[19]



The CSUR must attend to patients residing in its respective region under the same conditions and guarantees as to patients referred from other AACC[20]. Around 27% of RD patients in Spain have had to move from one AACC to another[4]. CSURs are financed by the Health Cohesion Fund which, until 2012, was financed by the Ministry of Health, Social Services and Equality. However, since the 2013 Budget Act, the source of funding for these funds has been modified, and they are now offset by the balance between the AACC and charged to the budgets of each region. Hence since then there is no state funding, and the CSUR are financed from the AACC funds[21].




In the European context, the directive on the application of patients' rights in cross-border healthcare was adopted in 2014, highlighting the importance of the establishment of European Reference Networks (ERN) and setting out the criteria for the establishment and evaluation of such networks, in order to facilitate the exchange of information and experience between them[22]. This system began its activity in 2017, encompassing 24 thematic networks (17 of them with spanish contribution) and with the participation of 300 hospitals and 900 healthcare centres from 26 countries, allowing healthcare professionals to access consolidated theoretical and practical knowledge on RDs, which would otherwise be fragmented in different countries[23].

### 3.4. RESEARCH

A major challenge in the field of RDs is their R&D process. As with other drugs, this can occur in two ways: the primary development of new molecular entities, or the repurposing of an existing drug for a rare or other disease. Despite advances, only 5-10% of RDs have a specific treatment available. On average, each new molecule marketed costs 1.5 billion euros and requires 7 million hours of research[24,25].

#### Challenges

Some specific challenges in the R&D of RD therapies are the lack of specialised information, the lack of networking, the lack of commercial attractiveness of the projects, the scarcity of resources, the lack of specialised centres and the difficulty of locating them, the heterogeneity of the diseases and the geographical dispersion of patients, among others. Currently, these difficulties are deepened by the potential impact of the coronavirus disease pandemic (COVID-19) on the health system and RD research.

Given these characteristics, clinical trial design often involves a number of difficulties related to smaller sample sizes, the impossibility of randomisation and the use of double-blind methodology, the use of comparators, the way outcomes are measured, the average duration of the studies or the adverse reactions observed (Table 6)[25–27].

**TABLE 6: COMPARISON OF CLINICAL TRIAL CHARACTERISTICS FOR RD-TARGETED THERAPIES VERSUS DRUGS FOR COMMON DISEASES**

**Source:** Rana (2018)[26]

| CHARACTERISTICS OF CLINICAL TRIALS | MEDICINES TARGETED AT RDs | MEDICINES TARGETING COMMON DISEASES |
|---|---|---|
| Sample size | Minor (n=96) | Major (n=290) |
| Randomisation | Less likely (30%) | Most common (80%) |
| Double blind | Less common (4%) | Common (33%) |
| Primary outcome variable | Measures disease response | Measures disease progression |
| Comparator | None in 70% of trials | Present in 80% of trials |
| Serious adverse events | Most frequent (48%) | Less frequent (36%) |
| Average trial duration | Shorter (5 years) | Longest (6.9 years) |

According to data from the RDs Resource Map (MAPER) of the Centre for Biomedical Research Network on RDs (CIBERER), 429 clinical trials for 212 RDs are currently underway in Spain, of which 60% are in phase III and 1% in phase IV. The 50 most investigated diseases (in 58% of trials) are aimed at developing treatments for cancer (57%), haematological diseases (14%), neurological diseases (8%), genetic diseases (6%) and others (15%)[28].

### Impact of research on funding and access

Several aspects of research could have a positive impact on the funding and access to RD therapies: the increase in the volume of activity through more trials; increased funding for research activity and increased support measures; aspects related to the generation, management, use and integration of data; or the innovative evolution of research activity itself, with personalised medicine, improved sequential methods of diagnosis or the intensification of telemedicine and mobile technologies.

## 3.5. INTERNATIONAL INTERNSHIPS

ODs must be compulsorily and centrally approved across the EU. Subsequently, it is the Member States who decide on their commercialisation and public funding in each country, resulting in differences in effective access to these therapies. In this regard, some good practices could be learned from neighbouring countries to facilitate funding and access to RD-targeted therapies, such as considering other funding criteria, establishing alternative evaluation and funding models, or using specific funds. Some milestones in Germany, France, England and Italy are reviewed below.



### Germany

Germany is a **paradigmatic case in terms of rapid access to new therapies**, which also affects RDs therapies. In Germany, funding decisions are mainly based on the clinical value of the therapy, having a greater laxity for clinical evidence in the case of RDs[29]. It is also one of the only countries that carries out its evaluations based on EU recommendations, with explicit reference to the EMA's Committee for Orphan Medicinal Products (COMP). Patient access to RD-targeted therapies is the fastest in Europe, as it allows an immediate reimbursement for medicines that have a lack of therapeutic alternatives[29,30]. While initially all therapies are automatically reimbursed, an assessment of the clinical benefit of the drug is carried out after 6 months, followed by a price negotiation

that can take 6 months[31]. If the drug's sales volume exceeds €50 million per year, the new negotiated price is applied, regardless of whether it is an orphan drug or not.

ODs do not need a comparator to determine their degree of added value: significant, considerable, minor or unquantifiable (when there is insufficient data to describe the extent)[32]. This country is **more flexible in relation to the decision criteria** and evaluates other elements, such as the rarity of the disease and whether the drug is intended for a specific population (e.g. children)[33].



### France

In France, ODs follow the same process as therapies indicated for more prevalent pathologies. After being authorised by the EMA, pricing and financing decisions are taken by the *Haute Autorité de Santé*, through a dual channel used by the Ministry of Health for negotiations with sponsors[34].

On the one hand, the therapeutic benefit of the drug (SMR) is assessed using a 4-level, 5-criteria system: severity of the disease, efficacy, adverse effects, expected position in the therapeutic strategy compared to other available therapies, and public health benefits. In addition, the **added therapeutic value of the drug (ASMR)** is **assessed in a 5-level system** that compares, in terms of efficacy and safety, the new therapy against available treatments. These criteria tend to benefit RD-targeted therapies. In fact, between 2000 and 2006, 40% of ODs received an ASMR between I and III, compared to 3% of all approved drugs in the country[35].

Under French law, the time between EMA approval and actual marketing is 6 months, although this period is rarely met[36]. In fact, the median time between authorisation and access to the drug is 360 days[34]. As an alternative methods, compassionate use is made of a procedure called ATU - temporary authorisation for use, prior to the pricing and financing decision, which has been used for 70% of the ODs reimbursed in the country[32].



### England

In England, RD therapies follow the same funding criteria as medicines indicated for prevalent diseases (incremental cost-effectiveness ratio and budgetary impact), although additional elements are taken into account.

For the assessment of therapies classified as ultra-orphan (prevalence <1/50,000 population), the National Institute for Health and Clinical Excellence (NICE) has been using the highly specialised technology approach since 2016, where access from EMA authorisation cannot exceed 20 months for new medicines and 15 months for new indications[37]. For these technologies, additional consideration is given to aspects such as the nature of the disease or the social impact of the technology, with explicit social values underpinning the process. If the therapy demonstrates significant QALY benefits, **NICE allows ultra-ODs a threshold of up to £300,000 per QALY (up to 10 times the standard threshold)**[33], while maintaining the annual budget impact limit of £20 million

in the first three years applies to all drugs in general[38]. In practice, the incremental cost-effectiveness ratios (ICERs) of ODs and ultra-ODs with a positive recommendation have an average ICER almost twice that of all other drugs, with values of £43-46k/ QALY vs. £24-25k/ QALY[39].

In addition, England applies a **fast-track** procedure for those medicines that the company indicates the ICER will not exceed £10,000 per quality-adjusted life year (QALY) gained,and the UK assessment agency believes that the ICER is unlikely to exceed £30,000/QALY[40] .

Promising cancer therapies (including orphan cancer drugs), but with uncertainty about their effect, have another access route through the Cancer Drugs Fund. This framework considers broader value criteria, such as the nature of the disease (severity, alternative therapies), social perspective and impacts beyond health benefits. It also uses a simpler and more tailored process in relation to the provision of evidence and specific evaluation committees[33].



### Italy

Italy has put in place various regulatory initiatives to facilitate access to ODs, related to financial protections for designated ODs, **fast-track** procedures, **early access to off-label drugs** (case-by-case prescription) and the conduct of independent research, through funding from the Italian Medicines Agency (AIFA).

Since 2007, Italy has been using a **specific algorithm to assess innovative medicines**, including those for RDs, which considers clinical efficacy, cost-effectiveness, budgetary impact and level of innovation. For RDs, they also assess the existence of alternative therapies and the extent of therapeutic effect, although the quality of evidence is low[41]. Once a therapy has been shown to be innovative and is accepted for reimbursement, it is financed from national budgets under the Innovative Medicines Fund or the Innovative Cancer Drugs Fund, as appropriate[42]. These funds have a total allocation of 1 billion euros per year, split 50/50 between both funds[43].

In addition, Italy stands out for its high use of managed entry financial schemes, which include two types of agreements, financial and performance-based, in some cases associated with price discounts depending on the indication[44].

## 3.6. CRITERIA FOR THE FUNDING OF RD-TARGETED THERAPIES

Countries generally take into account different criteria for the funding of RDs therapies, which can be grouped into the following groups[45]:

- **Clinical.** The most commonly used in routine practice. They include the unavailability of alternative therapies, the pathology severity and the ability of changing the course of the disease.

- **Economic.** These include factors such as budgetary impact, opportunity cost and

the sustainability of the health system as a whole. Some authors indicate that not only the economic impact of the treatment should be assessed, but also the social impact (loss of labour productivity, burden on carers, etc.) of funding, or not funding, the therapy in both the short and long term.

- **Humanistic.** Based on the concepts of equity and justice. They relate to the debate about equal access for RD patients, as opposed to the resource maximisation view, which argues that investment in non-cost-effective treatment for RDs means placing a higher value on improving the health of patients with RDs than that of patients with ordinary diseases. It also includes elements such as the "rule of rescue", which involves adopting a moral imperative to save a life that is in imminent danger, as a form of solidarity. Another potential humanistic criterion, although controversial, relates to the rarity or low prevalence of the disease targeted by the drug.

### 3.7. DETERMINANTS OF FUNDING AND ACCESS IN SPAIN

In Spain, RD therapies follow the same funding process as other therapies. The process begins with the support of the European CHMP, followed by the application for a National Code by the marketing laboratory. When the applicant communicates the intention to market the therapy in Spain, the AEMPS, in collaboration with the AACC and scientific societies, prepares a draft that is adopted by the Therapeutic Positioning Coordination Group. This group is responsible for preparing the Therapeutic Positioning Report (TPR), which helps to define the price and financing resolution[46].

The Directorate General for the Common Portfolio of Services of the NHS and Pharmacy (DGCSF) initiates the procedure to decide on price and financing. At this stage, the company provides the documentation required by the Ministry: a value dossier on the clinical contribution of the therapy, a budget impact analysis and a price and financing proposal (sometimes, it includes a cost-effectiveness analysis too[47]). This negotiation stage also contains the TPR (Figure 7)[48].

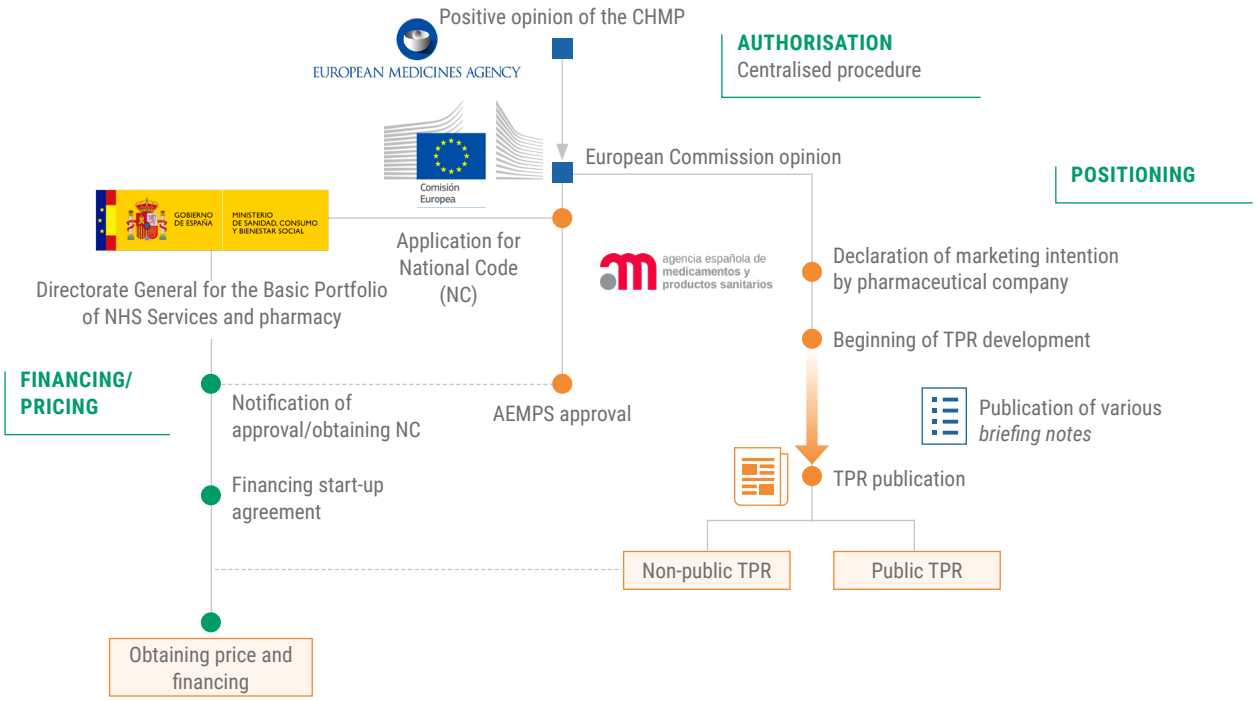



**FIGURE 7. ACCESS PROCESS FOR THERAPIES TARGETED AT RDs IN SPAIN**

**Note:**
**AEMPS:** Spanish Agency for Medicines and Health Products;
**CHMP:** Committee for Medicinal Products for Human Use;
**CN:** national code;
**EMA:** European Medicines Agency;
**TPR:** Therapeutic Positioning Report;
**SNS:** NHS;
**Source:** de Burgos (2019)[48]

Although there is no specific legislation on RD therapies, these medicines are affected by different regulations. For example, in relation to equity, it should be pointed out the Law 16/2003, on cohesion and quality of the NHS, which establishes that public health administrations must *"ensure citizens' right to health protection, with the common objective of guaranteeing equity, quality and social participation in the NHS"*[49]. Furthermore, according to RD-legislative 1/2015 of 24 July, which approves the consolidated text of Law 29/2006 on guarantees and rational use of medicines and health products, art. 91.5 states that *"measures aimed at rationalising the prescription and use of medicines and health products that may be adopted by the AACC shall not produce differences in access conditions, catalogue and drug prices and health products financed by the NHS"*. Similarly, art. 91.1 states that *"the citizens rights to obtain medicines under equal conditions throughout the NHS is recognised, without prejudice to the measures aimed at rationalising the prescription and use of medicines and health products that may be adopted by the AACC in the exercise of their competences"*[50].

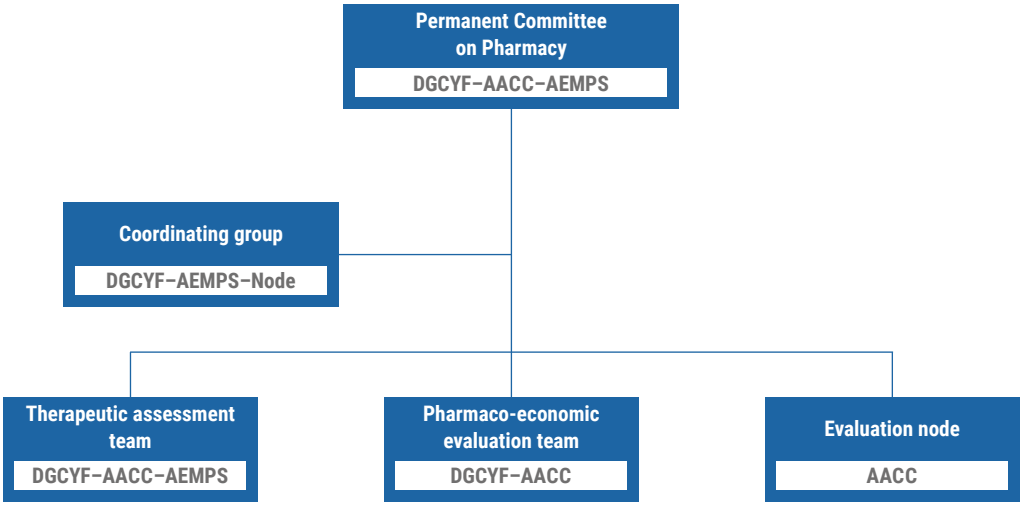
On the other hand, the Therapeutic Positioning Reports (TPR) are a fundamental part of access to medicines, which were introduced in 2013 as a support tool for funding decisions, by establishing the therapeutic position of the innovative medicine evaluated in comparison with available alternatives[46].

In November 2020, the Ministry of Health presented an TPR consolidation plan to improve the assessment process through changes in the governance and tools applied in the development of TPRs[51]. The plan has been developed around the following three action lines[52]:

1) Creation of the drug evaluation network, called REvalMED, which will consist of a therapeutic evaluation group, an economic evaluation group and seven evaluation nodes by clinical areas (one for non-oncological RDs and advanced therapies)[51]. In REvalMED, the NHS Standing Committee on Pharmacy focuses on the system's governance and general lines of action (Figure 8).

**FIGURE 8. STRUCTURE OF REvalMED**

**Source:** AEMPS (2020)[46]



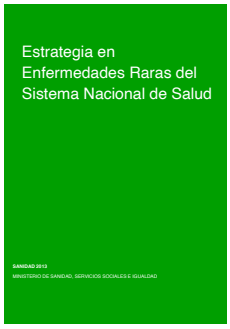

2) Modification of the design and approval methodology of TPRs. This includes a reordering of the elaboration of the TPRs based on a prioritisation matrix that streamlines the process when necessary[52]. In addition, twelve specific steps are established to ensure that reports are produced within a maximum of 90 days[52].

3) Development of a scorecard for the control and monitoring of TPRs, containing indicators relating to the time of each stage and the categorisation of the positioned medication[46].

Another fundamental change proposed in the new TPRs is the mandatory inclusion of economic evaluation as a compulsory input in the reports, whether in terms of cost-utility, cost-effectiveness or cost-minimisation analysis. The evaluation methodology developed by the Genesis Group of the Spanish Society of Hospital Pharmacy (SEFH), which in turn follows the RAND/UCLA methodology or appropriate use method, will be followed[53]. In general, the economic evaluation will take into account the health system perspective, imputing direct health costs only[53].

### Strategic plans in RDs

Moreover, RDs have a National Strategy and various regional strategies aimed at improving the prevention, diagnosis and healthcare of people suffering from them. In 2009, the Ministry of Health approved the first Strategic Plan on RDs, which aimed to improve the care and treatment of these diseases. The Strategy was updated in 2014 with 7 lines of action in order to re-evaluate the results obtained, adjusted to the new contexts[54]:




1. Information on RDs. Emphasis is placed on the importance of accurate information for professionals, patients and their families, for better diagnosis and care.

2. Prevention and early detection. Pointing to genetic diagnosis and neonatal screening programmes as the first line for rapid diagnosis.

3. Health care. Emphasis on rehabilitation and having CSUR.

4. Therapies. Genetic reference and off-label use of therapeutic alternatives.

5. Social and health care. Measures to improve social and health care (the System of Equal Opportunities for People with Disabilities as example).

6. Research. Importance of the flow of information between the different research networks, both at national and European level.

7. Training. Importance of the approach to RDs in the training process, both in Primary Care and in Hospitals.

In addition to the national strategy, several AACC have approved their own RDs plans (Figure 9)[55]. Five regions (Andalucia, Madrid, Extremadura, Navarra and Murcia) have their own specific strategic plans for RDs, and other regions, such as Catalonia, the Basque Country, the Valencian Community and Castilla La Mancha, have implemented other types of initiatives that directly affect RDs[56,57].

**FIGURE 9. EVOLUTION OF THE DIFFERENT AACC PLANS ON RDs, 2001-2021**

**Source:** own elaboration




## Key elements for funding

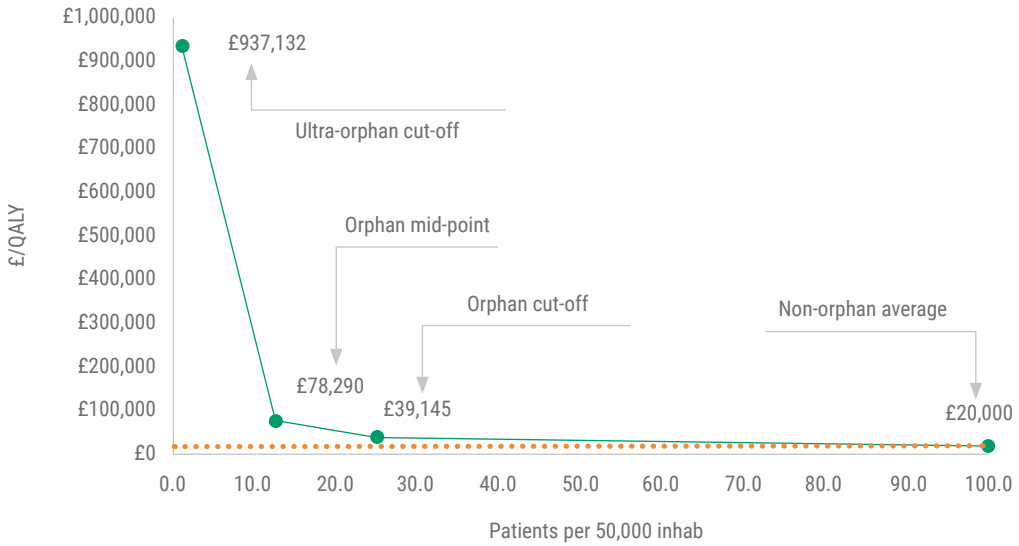
Funding therapies for RDs faces the challenge of balancing the uncertainty of the clinical benefit with the high cost per patient that these therapies often entail. In addition, it is difficult to capture the value associated with these therapies at the time of drug launch, and given the high price of these therapies, their funding would be less likely to be recommended as efficient. Despite this, RD therapies are approved even if they do not meet the efficiency criteria, given that other criteria are also taken into account[45].

## THEORETICAL THRESHOLDS FOR THE FUNDING OF ODs AND ULTRA-ORPHANS

A recent publication addresses what would be a reasonable price for an OD, proposing a way to adjust the cost-effectiveness threshold to account for differences in patient populations and R&D costs, in order to maintain prices that generate rates of return on investment in ODs development no higher than the industry average return[39]. They set as a reasonable cut-off point a threshold of around £39,000/AVAC for orphan and £937,000/AVAC for ultra-orphan (Figure 10).

**FIGURE 10. ADJUSTED COST-EFFECTIVENESS THRESHOLDS FOR DIFFERENT TYPES OF ODs MEDICINES**

**Source:** Berdud (2020)[39]




Other publications recommend not to have different thresholds for different pathologies or types of medicines, but to weight the different decision criteria differently[38,58].

In Spain, the law establishes that the public reimbursement of drugs is ruled by taking into account the following criteria (some of which would particularly affect RD patients)[50]:

**a)** Severity, duration and sequelae of the pathologies for which they are indicated.

**b)** Specific needs of certain groups.

**c)** Therapeutic and social value of the medicinal product and incremental clinical benefit of the medicinal product taking into account its cost-effectiveness.

**d)** Rationalisation of public expenditure on pharmaceuticals and the budgetary impact on the NHS.

**e)** Existence of medicines or other therapeutic alternatives for the same conditions at a lower price or lower cost of treatment.

**f)** Degree of innovation of the medicinal product.

In turn, RD-Law 8/2010 and RD-Law 9/2011, which adopted extraordinary measures to reduce public deficit and contribute to fiscal consolidation, considered the need for additional incentives for ODs, applying a 4% deduction on the retail price of medicines charged to the NHS pharmaceutical provision, compared to the 7.5% deduction made for other therapies[59,60].

Another noteworthy element is the exemption, as of the resolution of June 2 2020 of the Directorate General for the Common Portfolio of NHS Services and Pharmacy, from including ODs in the Reference Price System, as long as there is no therapeutic alternative, or, if there is, the orphan medicinal product provides a relevant clinical benefit. For this purpose, the available evidence and scientific knowledge, as well as the TPR, if any, will be considered[61]. This measure is taken in accordance with the European Parliament Regulation 141/2000 which promotes the research on orphan medicines.

**HEALTH COHESION FUND**

The Health Cohesion Fund, created by Law 21/2001 and regulated by RD 1207/2006 of October 20, aims to guarantee equal access to public health care services throughout Spain in order to reinforce the solidarity. It was initially endowed with €48.1 million[62,63]. Under the Health Cohesion Fund, the AACC were compensated for the health care services provided to, among others, patients resident in Spain who were referred between the AACC for care in the NHS reference centres, services and units, as a result of the application of techniques, technologies and procedures whose supervised use is authorised under article 22 of Law 16/2003.

Subsequently, Law 3/2017 modified some of its conditions, and the fund became the same extra-budgetary fund as the Welfare Guarantee Fund. In the 2019 General Budget, the fund had €3.76 million. Several articles of RD 1207/2006 were suspended from the 2021 General Budget Law, establishing the extra-budgetary nature of the fund, as well as the system for offsetting positive and negative balances arising from the healthcare expenses of patients referred between AACC[64].

With regard to financing formulas, traditional discounting models and price-volume agreements are simpler to use and the most commonly employed in practice[65,66]. However, there is a growing tendency to use more sophisticated schemes, especially when there is high uncertainty, as is the case for therapies targeting RDs. These include conditional reimbursement, payment by results, and deferred payment arrangements[67].

### Access at regional/hospital level

Once the medicine has been authorised and funded by the NHS, the next step is to access at the regional and hospital level. Some regions have centralised access schemes, while others have a decentralised scheme subject to approval by the Pharmacotherapeutic Commission (PTC) of each hospital, and others have a mixed system.

Decentralisation and the subsequent diverse methods of evaluation and funding in the different AACC and hospitals, along with the variation in actual prices and payment methods, can lead to inequalities in access within a region, both at the regional and hospital level[30]. Similarly, laboratories' lack of information on prices in other countries may increase such inequalities. This is despite the fact that the law guarantees the right of all patients to have equal access to the medicines included in the pharmaceutical provision of the NHS. At this point, it is also necessary to take into account the differential healthcare, organisational and economic-budgetary aspects of the different AACC, given the impact they have on many of these therapies.

### Monitoring of targeted therapies for RDs in Spain

A key part of developing funding models that need to be supported by evidence in real clinical practice is the development of patient data registries that capture key measures of efficacy and safety and allow to monitor the results. Comprehensive monitoring of real-life patient health and quality of life outcomes is essential for some funding schemes.

In addition, registries can play a key role in improving the care of patients with these pathologies by helping to describe the natural history of the disease and identifying appropriate clinical endpoints for clinical trials[68]. However, the development of registries for real-world data collection has limitations, such as the type of requirements imposed, the lack of involvement of patients and other stakeholders in their design, the lack of information on their actual usefulness, or the existence of conflicts of interest in their generation and approach[69].

In this regard, in 2015, the State Register of RDs was created to provide epidemiological information, guide health planning and management, and provide basic indicators for comparison between AACC and countries[70]. There are also different public registries, such as that of the ISCIII and the Spanish Network of RD Registries for Research (SpainRDR), as well as different regional registries.

In addition, VALTERMED, the NHS information system, is underway since 2019. Its objective is to provide optimal information for appropriate decision-making in the macro, meso and micro management of pharmaceutical provision, in the different stages of the medicine cycle, determining the therapeutic value in real clinical practice of the medicines used in the NHS. The variables to be recorded are established in the pharmacoclinical protocols, which are drawn up in a collaborative and multidisciplinary manner. The information is recorded by doctors or pharmacists in the NHS hospital[71].

By August 2021, VALTERMED has published 11 pharmacoclinical protocols: five in 2019, two in 2020 and two others in 2021. Seven of the protocols include drugs targeting RDs: 3 for cancer, 1 for complex fistulas caused by Crohn's disease, 1 for cystic fibrosis, 1 for hypophosphatemic rickets and 1 for retinal dystrophy associated with mutation in biallelic *RPE65*, while the four protocols with drugs not classified as ODs target severe severe atopic dermatitis, COVID-19, lung cancer and breast cancer[72].

### 3.8. THE ROLE OF PATIENTS AND PATIENT ORGANISATIONS

Misinformation and lack of knowledge in relation to RDs causes that it is often the patients themselves along with patients' associations, who bring together the greatest amount of information on the management and needs of their own pathologies. In this context, it becomes necessary to take their vision, experience and preferences into account when making decisions about their disease management. The role of patients' associations is particularly important in pathologies with lower awareness. Their work usually includes the dissemination of knowledge about RDs, the promotion of research and the pooling of patients with the same disease.

In addition to empowering and involving patients (especially the most vulnerable) in their own treatment and diagnosis, it is also important to empower and involve them in other decision-making processes related to medicines development, health technology assessment, clinical guidelines and regulatory processes development, and research. Patient inclusion in decision-making has produced positive outcomes, such as increased knowledge about the pathology, correct perception of the risk of each disease, choice-making in line with the values of each patient, and reduced sense of conflict generated during the process[73].

There are several successful examples of initiatives and projects related to the inclusion of patients with RDs in decision-making processes. One of these is the participation, since 2000, of three representatives of RDs patient associations in the Committee for Orphan Medicinal Products (COMP) of the EMA, which is responsible for the designation of orphan medicines, for advising on the development and implementation of an EU policy on orphan medicines, and for the development of detailed guidelines related to orphan medicines[9].

Another example of patient involvement in health technology assessment processes has been carried out by NICE in the UK for two decades[74]. NICE involves patients, service users, carers and the general public in the various stages of the evaluation, evidence gathering and recommendation making process[29,30,75]. Currently, patients are involved in half of the 8 groups responsible for the evaluation process for new medicines[76]. Their role is to provide evidence, comment on draft technical reports, clarify questions about the evidence presented, and provide input before and after meetings. They can also appeal against the recommendations in the final assessment document before it is formally approved[76].

#### PATIENT PARTICIPATION IN EVALUATION PROCESSES

The European Patients' Academy (EUPATI), in its "Guidance for patient involvement in health technology assessment (HTA) processes", suggests a number of activities[77]:

- **Dissemination and training:** developing guidance materials on the different roles that patients can play in HTA processes; elaborating presentations and training workshops; etc.
- **Increased participation:** include patients in consultations on changes in evaluation processes, considering the use of participatory methods and including patients as

full members.

- **Identification and prioritisation of technologies to be evaluated:** develop a system for patients to nominate HTA technologies.
- **Scoping:** consult with patient organisations on the draft assessment and invite them to the oral consultation meetings.
- **Assessment and development of recommendations:** invite patient organisations to nominate patient experts and clinical experts to attend HTA committee meetings; assist and train them to act in this capacity.
- **Review and dissemination of HTA results:** summarise patient inputs in the results' document and indicate how they were used to arrive at the final recommendation. Provide non-technical language versions by inviting to include comments.

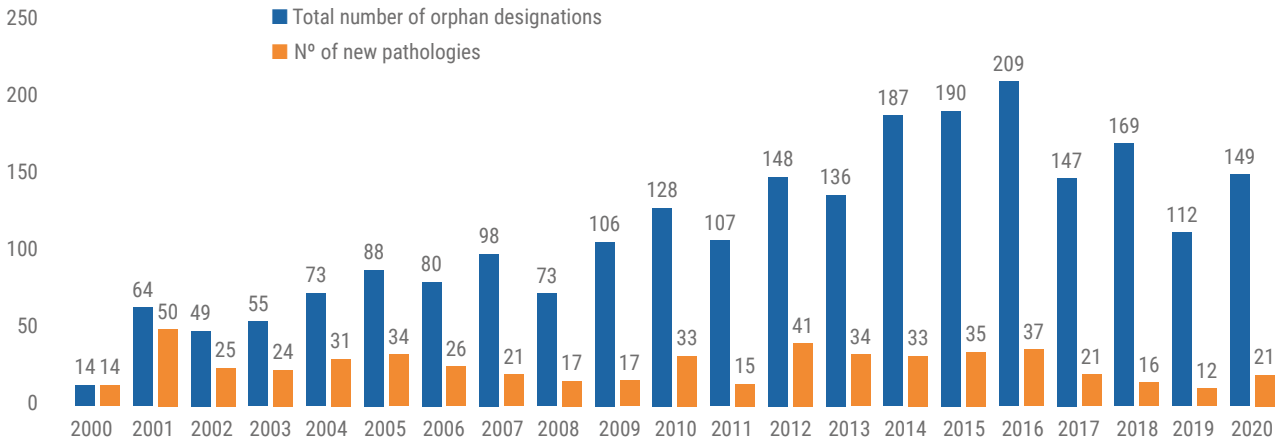
## 3.9. AUTHORISATIONS AND ODs COMMERCIALIZATION TIMES

### Designations and authorisations of ODs in Europe

Regulation around targeted therapies for RDs has had a clear impact on the evolution of the number of approved therapies in this field. Between 2000 and 2020, the EMA approved more than 2,300 orphan designations for 557 different RDs (Figure 11)[78]. With regard to the prevalence of RDs with orphan designation, 48% were pathologies with prevalence between 1 and 3 patients per 10,000 inhabitants, while 40% are ultra-rare pathologies (prevalence < 1/10,000 inhabitants) and the remaining 12% are pathologies with prevalence greater than 3/10,000 inhabitants[78].

**FIGURE 11. ORPHAN DESIGNATIONS AND NUMBER OF RDs THEY ENCOMPASS, 2000-2020**

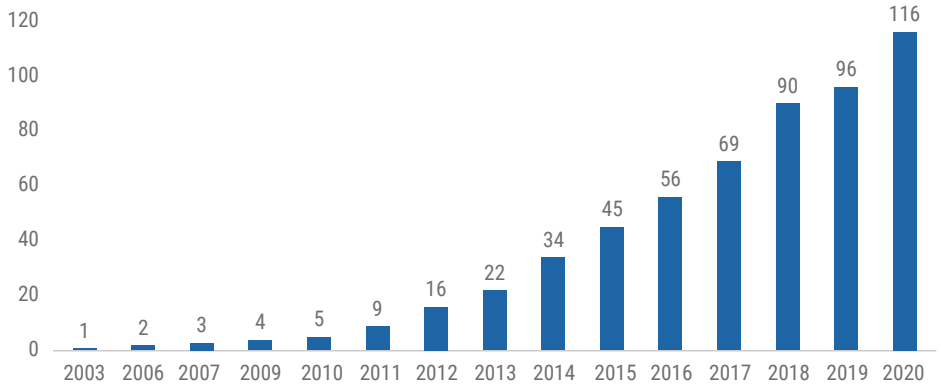
**Source:** EMA (2020)[78]



The last two decades have also seen a significant increase in the number of EMA-approved ODs. Currently, a total of 116 drugs remain in force as ODs (it should be noted that some ODs lose their designation prematurely, either because the designation expires or for other reasons). During 2020, 20 new ODs were approved, the second highest number of approvals in the year (Figure 12)[3].

**FIGURE 12. EMA-APPROVED ODs CURRENTLY IN FORCE, BY DATE OF APPROVAL, 2003-2020**

**Source:** own elaboration based on EMA (2021)[3]




## Effective access to targeted therapies for RDs

Spain occupies an intermediate position in terms of the level of access and the time taken to RD therapies access in Europe, although it is behind the countries in our closest economic and geographical environment (EU-12). Of the 116 ODs currently approved by the EMA, 51 (44%) have a marketing authorisation in Spain. In turn, 46 (40%) are financed by the Spanish NHS[5].

**FIGURE 13. AVAILABILITY OF EMA-APPROVED NON-ONCOLOGY ODs IN 2015-2018**

**Source:** IQVIA (2020)[80]

- Public availability
- Limited availability
- Only available privately
- Not available

According to a study analysing the 143 ODs approved by the EMA during the period 2000-2016, Germany approved 93% of them, being the country with the highest level of availability[79]. Among the countries analysed, followed by France (81%) and Italy (58.7%), while Spain approved 75 ODs, or 52%. Meanwhile, according to another recent study, based on the 39 non-oncology ODs approved between 2015 and 2018, Spain ranked 17th in the EU-28 in terms of access, with 26% of them available, compared to 95% in Germany, 66% in France and 62% in Italy (Figure 13)[80].

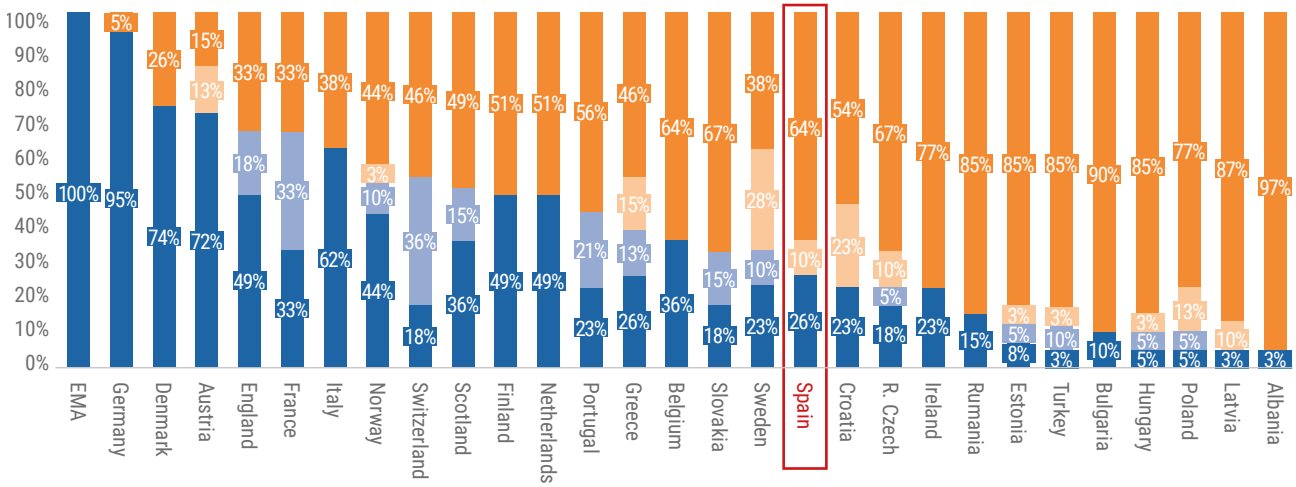
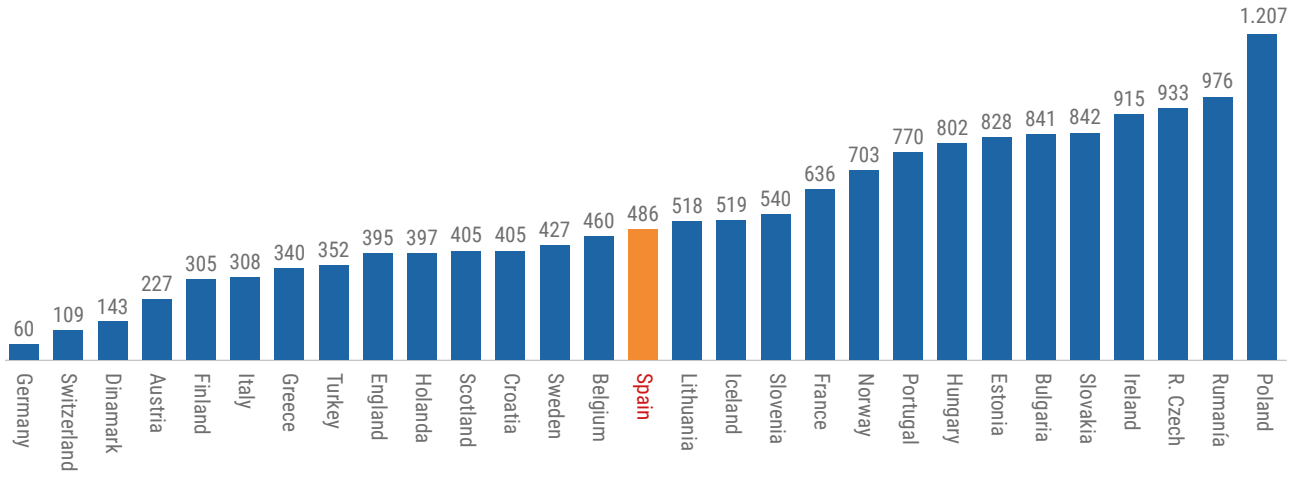


**FIGURE 14. MEDIAN TIME (IN DAYS) BETWEEN EMA AUTHORISATION AND ACTUAL AVAILABILITY IN THE COUNTRY, FOR NON-ONCOLOGY ODs APPROVED IN 2015-2018**

**Source: IQVIA (2020)**[80]

An important part of access is the speed with which treatments are available to patients. In this respect, several studies have analysed the time between approval by the EMA and the actual availability of the drug in the country. Germany also leads access to ODs, as in principle all medicines are automatically reimbursed upfront as soon as the therapy is approved. Apart from this exceptional case, Denmark, Austria, Finland and Italy are the countries with the fastest access, with a time lag between 109 and 308 days until the actual availability of the orphan drug in the country, while Spain has a median of 486 days (or 16.2 months) (Figure 14)[80].




In the case of Spain, another analysis carried out up to December 2017 indicates that the average time between approval (obtaining a national code) and the actual commercialization of ODs in our country was 20.1 months (with a median of 13.4 months)[81]. In addition, there is a high variability of times between different medicines, with a minimum interval of 2 months and a maximum of 91 months (7.6 years)[81].

## 3.10. FUTURE ORIENTATIONS

The main public awareness of RDs has been translated into greater political support. In our country, different parliamentary groups have presented proposals to review the incentives in force and promote actions of different depths, including greater integration, prioritisation and support, among others[82–84].

In Europe, the European Commission has opened a public consultation to review the current legislation on the development of medicines for children and RDs, in order to correct inconsistencies in the current legislation[15]. The review includes a new definition of ODs, introducing incidence as a criterion for identifying specific RDs, modifying market exclusivity for ODs and the requirements for eligibility, as well as providing new incentives, especially for paediatric ODs.

In order to define this incentive changes for RDs, several initiatives have been carried out, including the Rare2030 Plan, which has recently proposed eight recommendations as a reference for a new generation of European national plans and strategies over the next 10 years[85]. The project, initiated by the European Parliament, led by EURORDIS and co-

funded by the European Commission's Preparatory Actions Programme and Pilot Project, was carried out over the past 3 years by more than 200 experts and thousands of RDs patients[85].

Rare2030 recommendations include, among others, better coordination at European level, increased accuracy and reduced diagnostic times, more accessible therapies (more funded drugs) and affordability (lower prices), and equitable care including cross-border and virtual care, reduction of psychological, social and economic vulnerability, R&D driven by unmet needs, and better integration and availability of data (Figure 15)[85].

**FIGURA 15. RARE2030 PLAN RECOMMENDATIONS FOR THE NEXT 10 YEARS**

**Source:** Kole (2020)[85]

| | RECOMMENDATION | MAIN PROPOSALS |
|---|---|---|
| 1 | **Long-term visionary plans, integrated at European and national level** | • Prioritisation of RDs<br>• Coordinated actions at European and national level<br>• Long-term vision |
| 2 | **Earlier, faster and more accurate diagnosis** | • Diagnosis 6 months after medical consultation<br>• Access to technologies, best practices and effective diagnostic programmes<br>• Coordinated process at European and global level for the undiagnosed |
| 3 | **Access to high quality health care** | • Quality medical care<br>• As close to home as possible, with the possibility of physical or remote cross-border care |
| 4 | **Integrated and person-centred care** | • To reduce the level of psychological, social and economic vulnerability of people with a RDs and their families by one third |
| 5 | **Partnership with patients** | • Ecosystem fostering patient associations<br>• Spirit of co-creation<br>• Empowerment |
| 6 | **R&D based on unmet needs** | • Faster development and safer use of health innovations<br>• Improved organisation and management of holistic care and support |
| 7 | **Optimisation of data for patient and societal benefit** | • Correct coding and nomenclature of RD<br>• Accessible, interoperable and reusable data<br>• Integrated data at national and European level |
| 8 | **Available, accessible and affordable treatments** | • Safe, effective and affordable medicines<br>• Europe, a world leader in the development of therapies for RDs<br>• 1,000 new medicines available by 2030<br>• Therapies 3 to 5 times more affordable than currently available treatments |

### THE EUROPEAN PHARMACEUTICAL STRATEGY

Another future trend in incentives for RDs is the European Pharmaceutical Strategy, adopted by the European Commission in November 2020 to ensure patients' access to safe, effective and high quality medicines, while fostering the global competitiveness of the sector as a pillar of the European economy. The Strategy proposes 4 objectives, including ensuring access to affordable medicines, supporting competitiveness, improving crisis response mechanisms and ensuring a strong EU voice in the world[86].

The plan includes a number of priority actions, both legislative and non-legislative, which will focus on pharmaceuticals. The strategy advocates the need to break down the inability to work efficiently as a network, so that the different public authorities responsible for authorisation, evaluation, provision and financing work together.

It is also committed to harnessing the potential of new technologies and digitization, for which secure and efficient access to health data is key. To this end, the Commission will propose a European health data space and establish an interoperable data access infrastructure, which will improve the exchange, access and cross-border analysis of health data in the EU.

The Strategy mentions that a reflection process has been launched on how to best adapt the incentive system provided by the EU pharmaceuticals framework to stimulate innovation in areas where there are unmet medical needs (e.g. neurodegenerative and RDs and childhood cancers). In line with the principles for better regulation, the conclusions of the study on pharmaceutical incentives and the evaluation of the legislation on RDs medicines will determine any future review, scheduled for 2022[86].

Finally, it is worth remembering that the European Commission has agreed on the NextGenerationEU, a recovery plan to repair the economic and social damage caused by the coronavirus pandemic, which will have the largest EU funded incentive (1.8 trillion euros)[87], 140 billion of which will be earmarked for Spain over 2021-2023. Science, innovation and the reinforcement of the NHS are one of the 10 driving policies to which these funds will be allocated[88]. This opens the door to improvements and modernisations that could be applied to RD therapies.

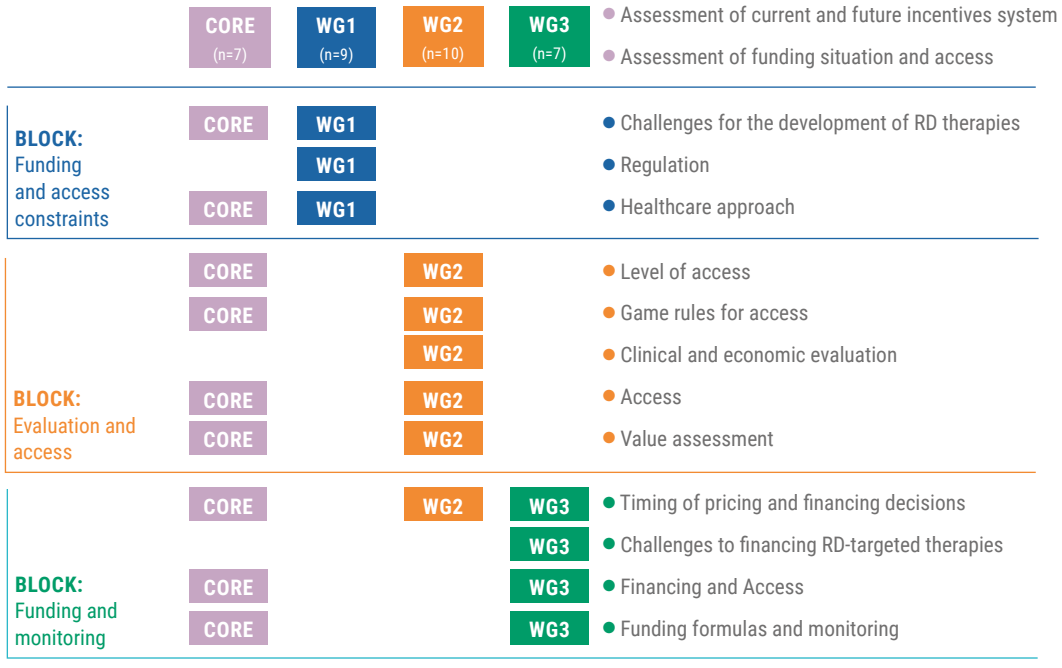
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# DIAGNOSIS OF THE CURRENT SITUATION

Prior to the meetings of the CORE Group and the first three WGs, experts were asked to answer a short online questionnaire in order to make an initial diagnosis of the current situation in the field of medicines for RDs in Spain. This diagnosis included both general questions and specific questions on issues to be addressed in the different WGs. Therefore, some questions were asked in more than one working group, while others were only posed to the experts of a certain group.

Let us remember that, in general terms, the CORE Group was responsible for the overall vision, WG1 for funding and access conditions, WG2 for the evaluation and access of medicines for RDs, and WG3 for the funding of these therapies. To better understand the dynamics, Figure 16 shows the relationship between the different topics covered in the diagnosis, and the groups that discussed these topics.

**FIGURE 16. OUTLINE OF THE TOPICS INCLUDED IN THE DIAGNOSIS OF THE SITUATION, BY WG AND BLOCK**

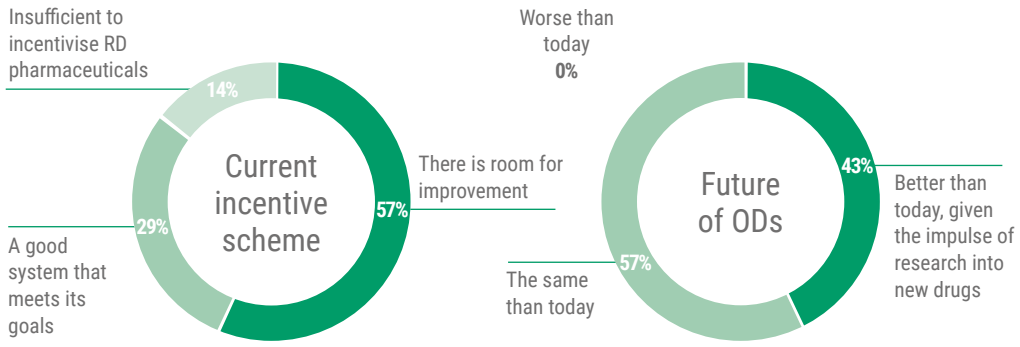


## CORE GROUP DIAGNOSIS

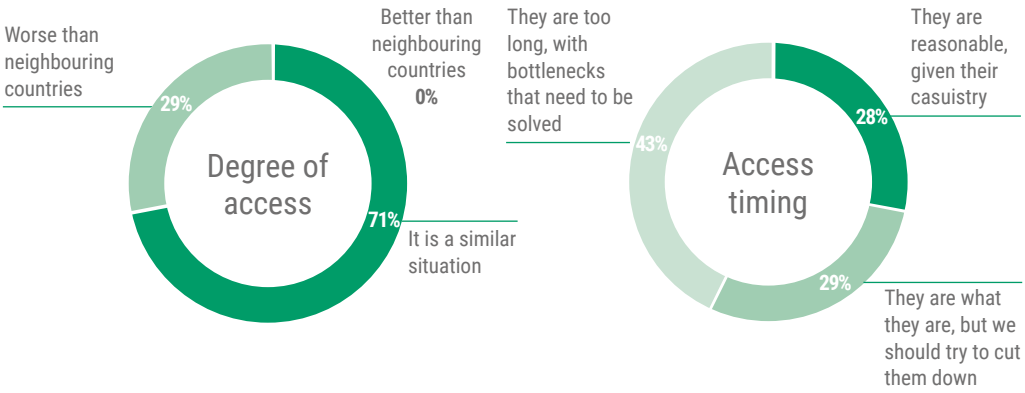
The CORE Group provided a comprehensive overview of the baseline situation of therapies for RDs in the NHS, giving opinions on both general and specific aspects, which were subsequently addressed in the different thematic blocks of each WG.

The majority of CORE experts (71%) agreed that economic problems are the main challenge facing these therapies, while for two experts the main stumbling block comes from the lack of comprehensive patient care and coordinated management. For their part, 29% believed that the main problem for developing new drugs in RDs is the lack of business incentives to invest, while the other 29% believed it was due to the difficulties in conducting clinical trials. Others mentioned the lack of public-private collaboration and the high uncertainty of health outcomes.

Regarding the current system of incentives for the development of RD-targeted therapies, more than half (57%) of CORE believed that there is room for improvement, while 29% believed the system is adequate and 14% that it is insufficient. Looking to the future, 57% thought the situation will be similar to today, and 43% thought it will improve, thanks to R&D in new drugs. None believed that the situation will get worse.

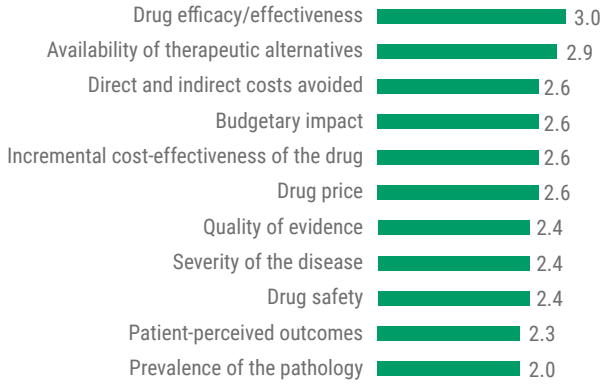



With regard to access to these therapies in the Spanish NHS compared to other countries, 71% believed that our situation is similar, while 29% considered that it is worse, and none that it is better. Forty-three percent indicated that the financing process in Spain takes too long, and 28% that it is reasonable, given the casuistry.




When asked whether RD therapies should be treated under the same rules as mainstream therapies, the majority of CORE group members (57%) believed that, given their particularities, they should be treated under certain specific evaluation and funding conditions, while 43%

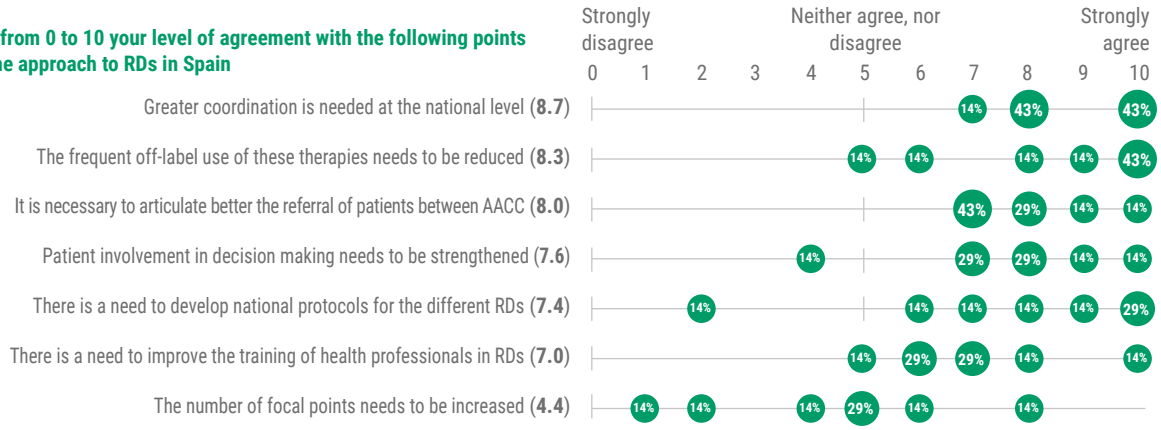
believed that they should be evaluated in a differential way, but being governed by the same pricing and funding conditions as other therapies. None of the experts considered that they should be treated in exactly the same way. There was no consensus on the desirability of a differential threshold of willingness to pay for these therapies (57% yes vs. 43% no).




For their part, the experts ranked the criteria to be considered when approving the funding of a medicine for a RD based on their relative importance or degree of impact, with efficacy/effectiveness and availability of alternatives being the most valued elements, and the prevalence of the pathology being of lesser relative importance.

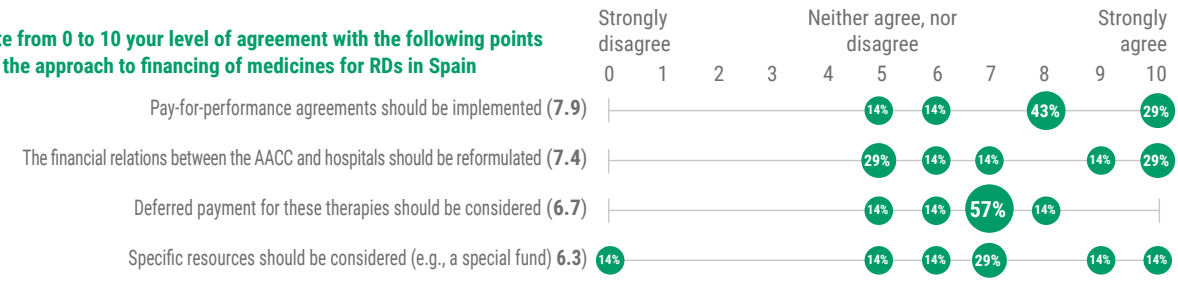
Regarding the approach to RDs in Spain, they agreed that greater coordination at national level is necessary, as well as reducing the off-label use of these therapies and better articulating referral between AACC. On the other hand, they disagreed on whether it is necessary to increase the number of reference centres.

**Please rate from 0 to 10 your level of agreement with the following points regarding the approach to RDs in Spain**



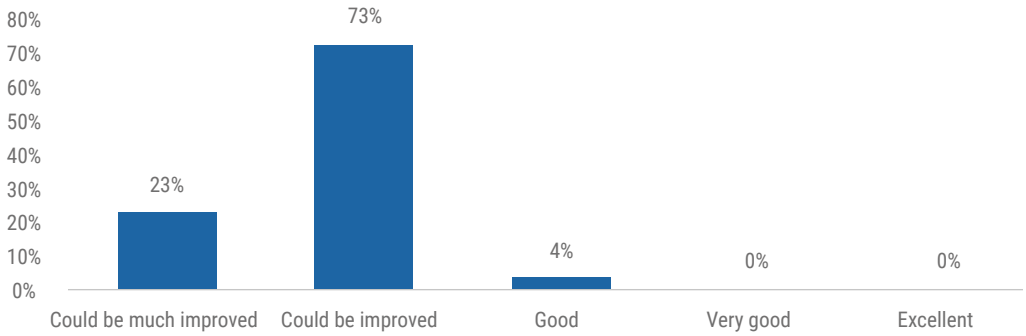

Regarding the financing of these therapies, experts agreed on payment-by-results systems, while they disagreed on whether to establish a specific fund for these medicines or to consider deferred payment.

**Please rate from 0 to 10 your level of agreement with the following points regarding the approach to financing of medicines for RDs in Spain**



Before addressing the initial diagnosis in the three thematic blocks, 73% of the experts in the three first WGs assessed the situation of funding and access to these therapies as improvable, and 23% as very improvable (Figure 17).

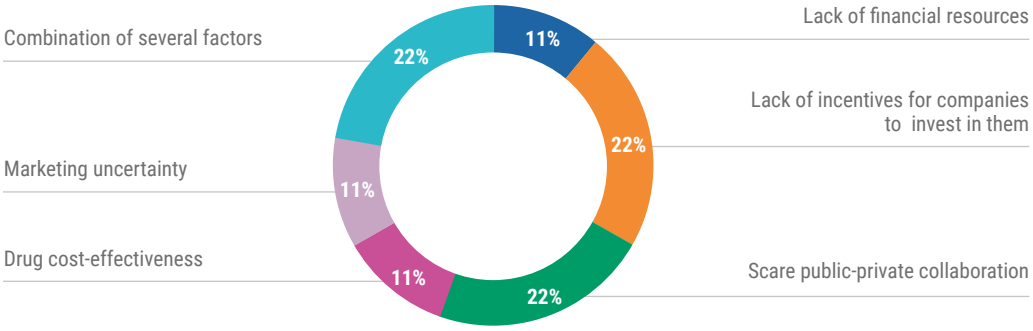
**FIGURE 17. WHAT DO YOU THINK ABOUT THE CURRENT SITUATION OF FUNDING AND ACCESS TO RD THERAPIES IN SPAIN? (N=26)**




## 4.1. FUNDING AND ACCESS CONSTRAINTS

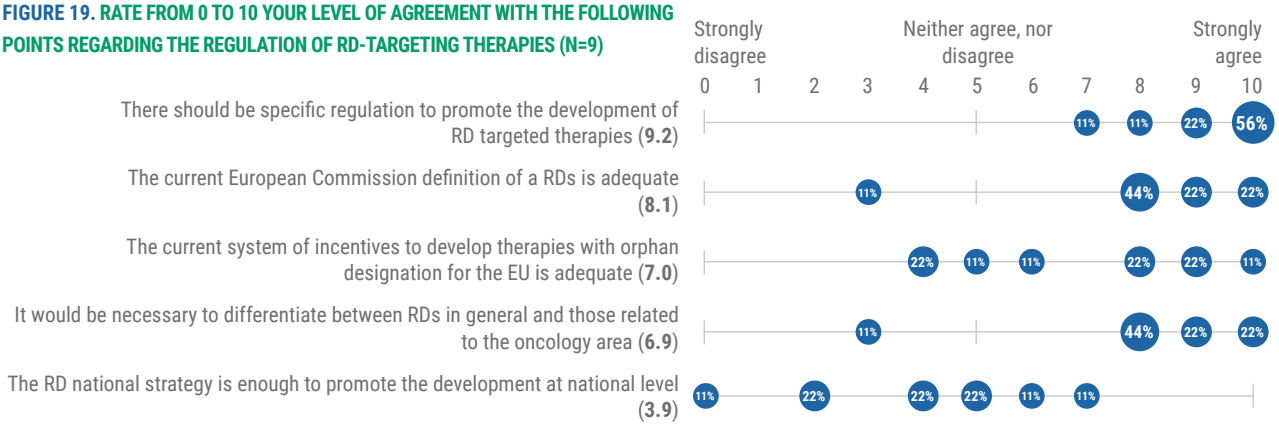
WG1 experts disagreed on the main challenge for the development of new therapies in RDs, as they considered up to 6 different challenges. Lack of incentives for companies to invest and poor public-private collaboration were the two main problems identified (22% both), a view that was in line with that of the CORE group. However, this group also highlighted other challenges, such as lack of financial resources, drug cost-effectiveness, uncertainty in commercialization conditions, and a combination of different aspects, ranging from trial design to incentives demanded by companies that clash with the sustainability of the health system (Figure 18).

**FIGURE 18 WHAT DO YOU THINK IS THE MAIN PROBLEM IN DEVELOPING NEW DRUGS IN RDs? (N=9)**



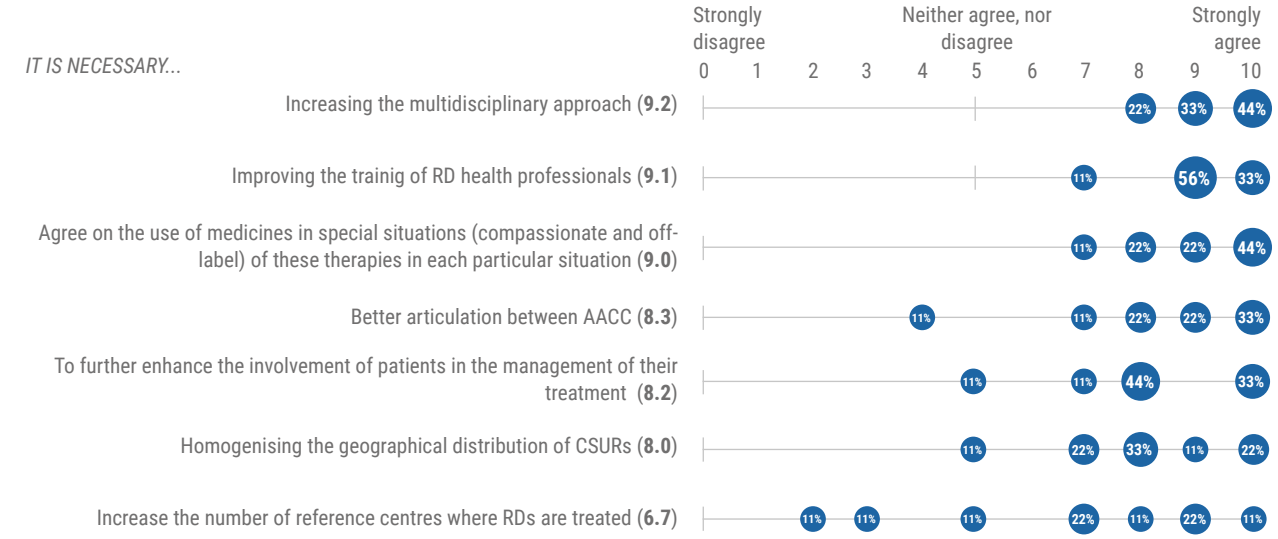

In general terms, the experts consulted agreed that there should be specific regulation for the development of RD therapies, and that the National Strategy for RDs is insufficient to promote the development of these therapies at national level (Figure 19). At the same time, they disagreed on whether the current European incentives system is adequate, or whether the definition of RD should be modified.

**FIGURE 19. RATE FROM 0 TO 10 YOUR LEVEL OF AGREEMENT WITH THE FOLLOWING POINTS REGARDING THE REGULATION OF RD-TARGETING THERAPIES (N=9)**




Regarding the healthcare approach to these therapies in Spain, most WG1 experts agreed on the need to increase the multidisciplinary approach, improve the training of healthcare professionals and reach a consensus on the use in special situations in each particular situation. As in CORE, there was less consensus on the need to increase the number of reference centres or to homogenise their distribution (Figure 20).

**FIGURE 20. RATE FROM 0 TO 10 YOUR DEGREE OF AGREEMENT WITH THE FOLLOWING POINTS REGARDING THE CARE APPROACH TO RDs IN SPAIN (N=9)**




## 4.2. EVALUATION AND ACCESS

Before interpreting the responses in this section, it is important to highlight that the TPR consolidation plan was published in November 2020, i.e. in the middle of the process of holding the FINEERR WGs. Therefore, the first groups (WG1 and WG2) carried out their diagnosis of the situation and recommendations for action without taking into account the new governance proposed by the Ministry, while WG3 and WG4 worked on the measures knowing this new perspective.

With regard to the relative access to RD therapies in the NHS compared toother European countries, 40% of WG2 experts believed that the degree of access is similar, and another 40% that it is worse, while 20% (2 experts) considered that it is better than in other countries in our environment (Figure 21), thus being relatively aligned with the CORE Group's opinion.

**FIGURE 21 HOW DO YOU THINK THE DEGREE OF ACCESS TO THERAPIES FOR RDs IS CURRENTLY IN SPAIN COMPARED TO OTHER COUNTRIES IN THE REGION? (N=10)**

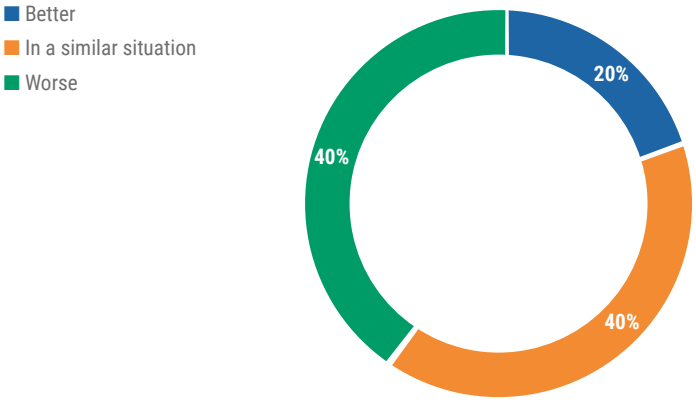



**FIGURE 22. RATE FROM 0 TO 10 YOUR LEVEL OF AGREEMENT WITH THE FOLLOWING POINTS REGARDING THE CLINICAL EVALUATION OF RD THERAPIES (0 BEING THE MINIMUM AND 10 THE MAXIMUM) (N=10)**

Regarding the clinical assessment of these therapies, WG2 experts generally felt that there should be greater agreement on the clinical uncertainty reported in TPRs for these drugs, and on what would be acceptable to obtain price and reimbursement relative to other drugs (mean 7.4 points). WG2 members disagreed on whether the assessment methods for these therapies should be differentiated from those for other drugs, as the CORE group think, or whether TPRs are more useful tools for pricing and financing decisions for these drugs than for other drugs (Figure 22). In any case, it should be taken into account that these opinions come before the publication of the TPRs consolidation plan in the NHS.

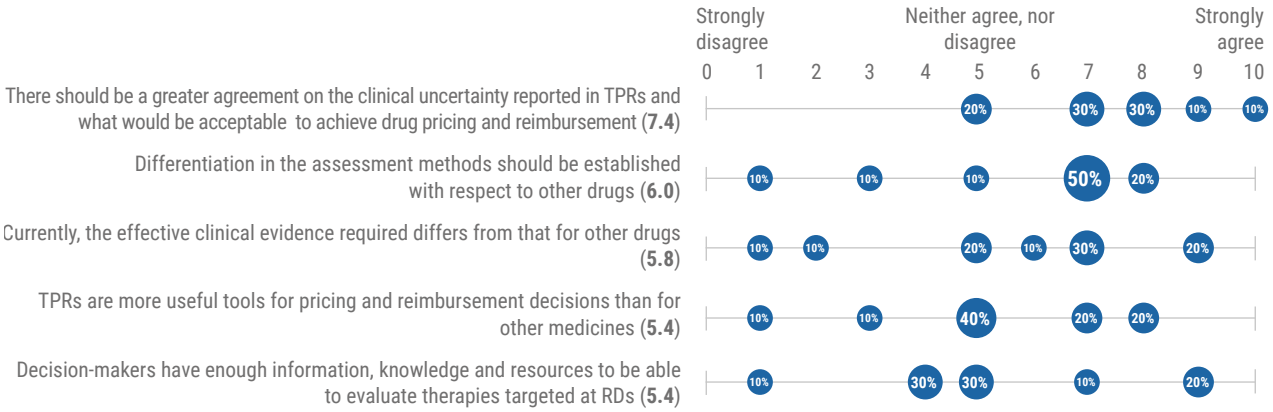


**FIGURE 23. RATE FROM 0 TO 10 YOUR LEVEL OF AGREEMENT WITH THE FOLLOWING POINTS REGARDING THE ECONOMIC EVALUATION OF RD-TARGETING THERAPIES (0 MINIMUM AND 10 MAXIMUM) (N=10)**

Regarding the economic evaluation of RD therapies, the majority of WG2 agreed that evaluations should use the societal perspective, and not only the payer's perspective, and that the patient should be more involved in the therapy evaluation process. On the other hand, opinions were more diverse regarding a possible differentiation of RDs in evaluation and uncertainty management (Figure 23).

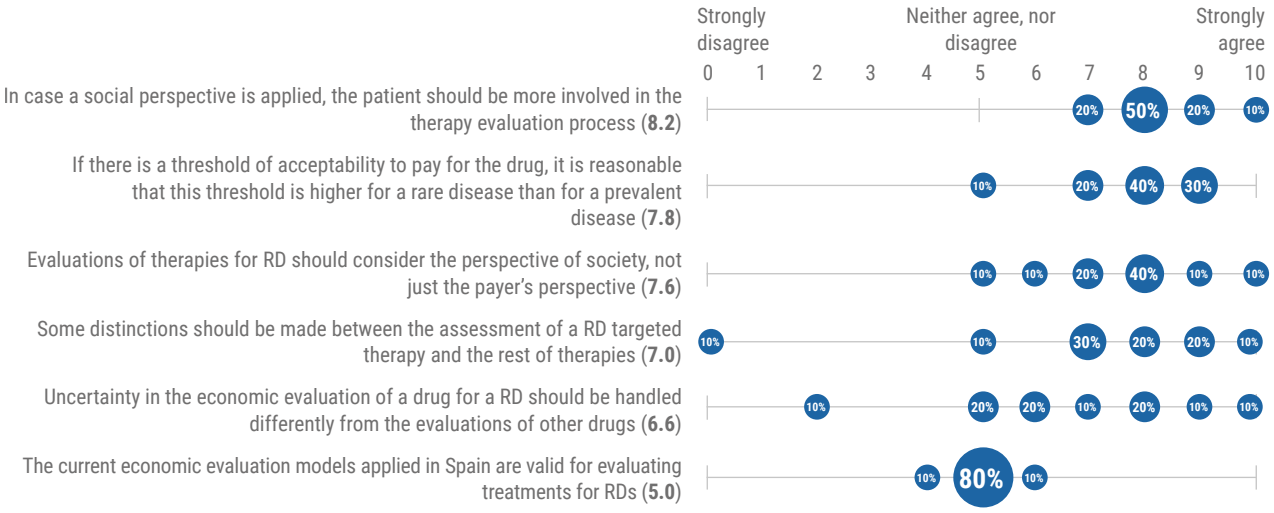
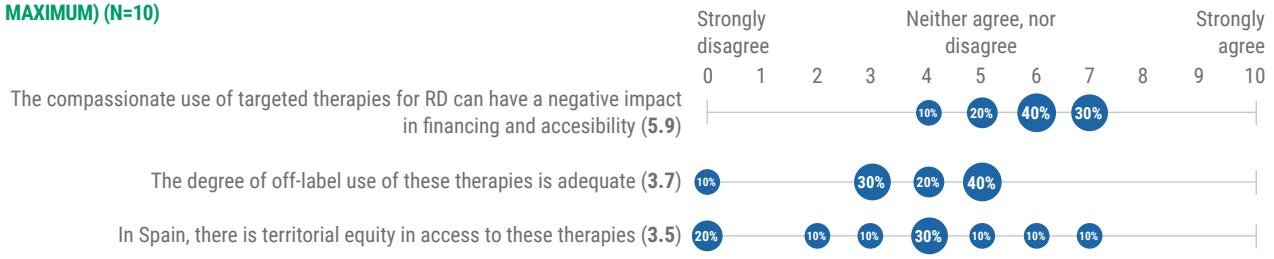


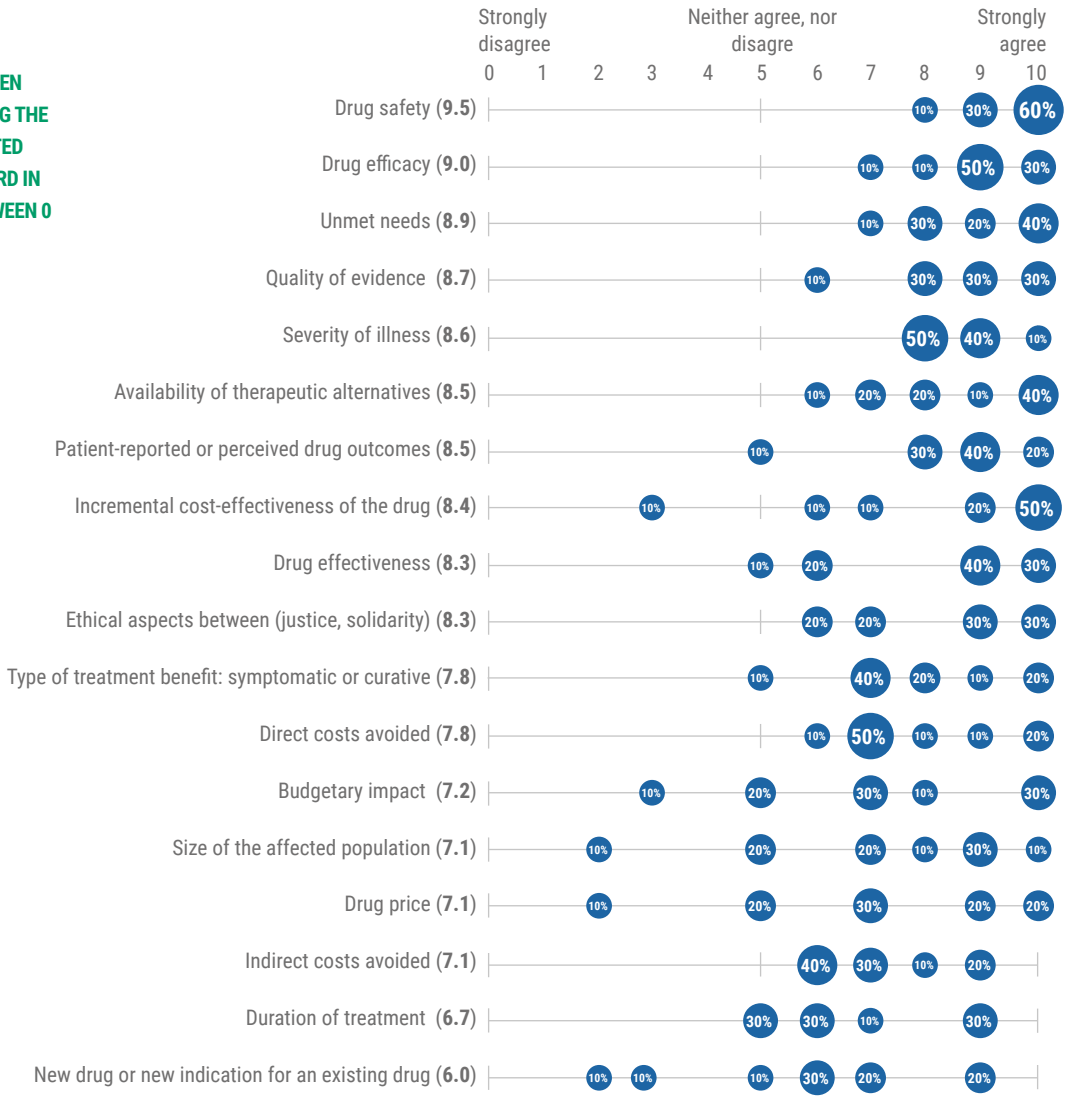

**FIGURE 24. RATE FROM 0 TO 10 YOUR DEGREE OF AGREEMENT WITH THE FOLLOWING POINTS REGARDING ACCESS TO THERAPIES FOR RDs IN SPAIN (0 BEING THE MINIMUM AND 10 THE MAXIMUM) (N=10)**

For their part, most WG2 experts did not agree that the off-label use of these therapies is appropriate. There was no consensus among them on whether or not there is territorial equity in access to these therapies in Spain. On the other hand, there was greater agreement on the possible negative impact that compassionate use of RD therapies may have on their financing and access (Figure 24).




Finally, experts were asked about the criteria that should be considered when assessing the value of these therapies in a broad sense. The criteria with the highest level of support and consensus were the safety and efficacy of the drug, followed by unmet need (remember that efficacy and existing alternatives were the most relevant for the CORE). WG2 experts also gave relatively high importance to quality of evidence, severity of disease, availability of alternatives and patient-reported outcomes (PROMs). In contrast, the least valued elements were novelty of therapy or indication, and duration of treatment. The lowest consensus was on the criteria of novelty, price and size of the affected population (Figure 25).

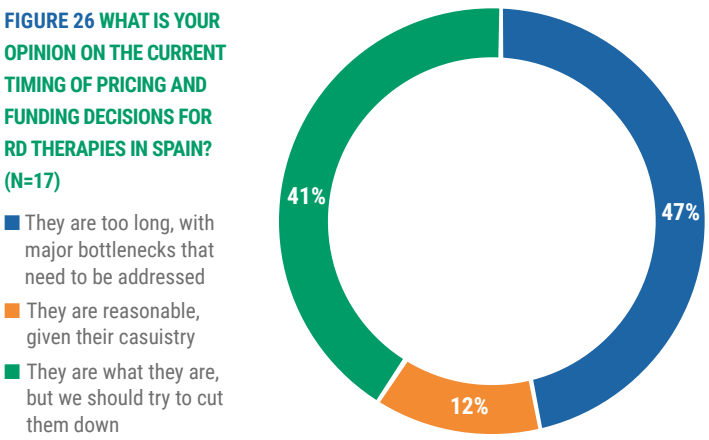
**FIGURE 25. WHAT ELEMENTS SHOULD BE CONSIDERED WHEN BROADLY ASSESSING THE VALUE OF A TARGETED TREATMENT FOR A RD IN SPAIN (SCORE BETWEEN 0 AND 10) (N=10)**



### 4.3. FUNDING AND MONITORING

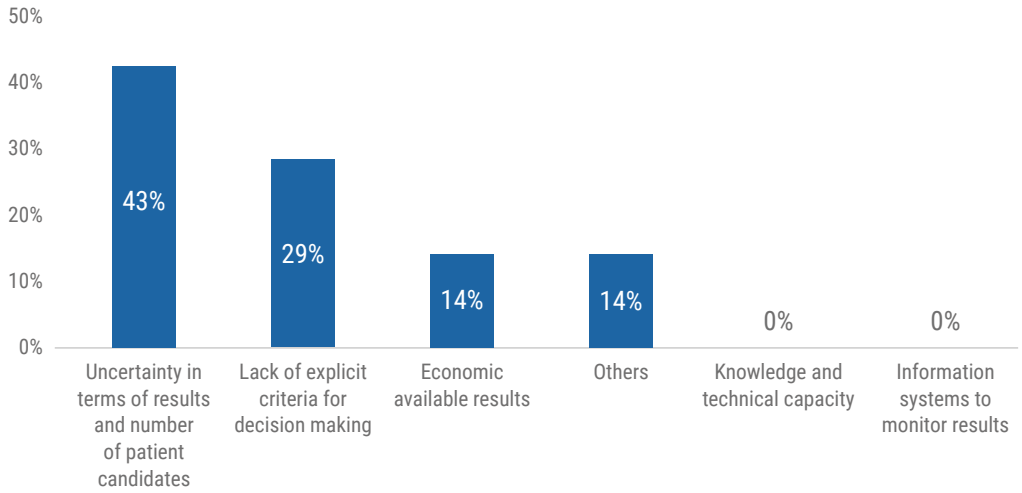
The majority (47%) of the experts (WG2 + WG3) thought, as the CORE, that the current pricing and financing decision times for therapies targeting RDs are too long and have significant bottlenecks to overcome, while 12% believed that they are reasonable, given their casuistry (Figure 26).

**FIGURE 26 WHAT IS YOUR OPINION ON THE CURRENT TIMING OF PRICING AND FUNDING DECISIONS FOR RD THERAPIES IN SPAIN? (N=17)**



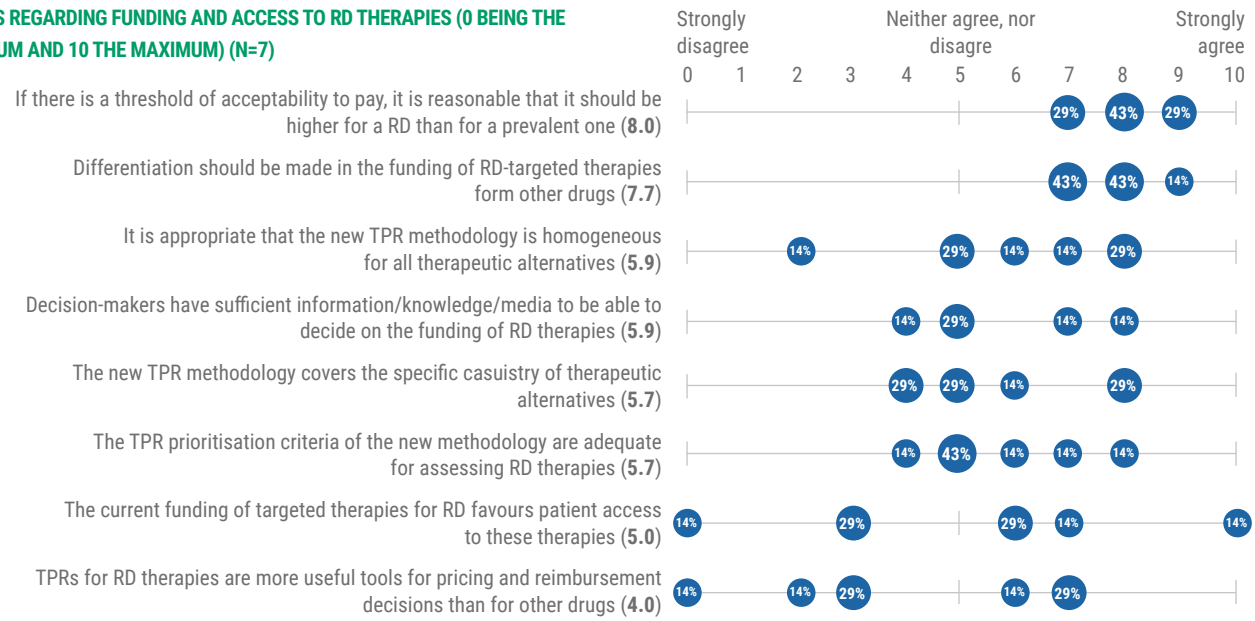

As for the main challenge in the financing of these therapies, there was no consensus among the WG3 experts. For 3 of the 7 experts (43%), the most important challenge is uncertainty in terms of outcomes and number of patients, followed by the lack of explicit criteria for decision-making (29%) and available financial resources (14%) (Figura 27). One of the experts was of the opinion that the main challenge comes from the combination of available resources and the lack of explicit criteria for funding.

**FIGURE 27. ACCORDING TO YOUR EXPERIENCE OR BASED ON YOUR VISION, WHAT DO YOU CONSIDER TO BE THE MAIN CHALLENGE IN THE FINANCING OF RD-TARGETED THERAPIES? (N=7)**



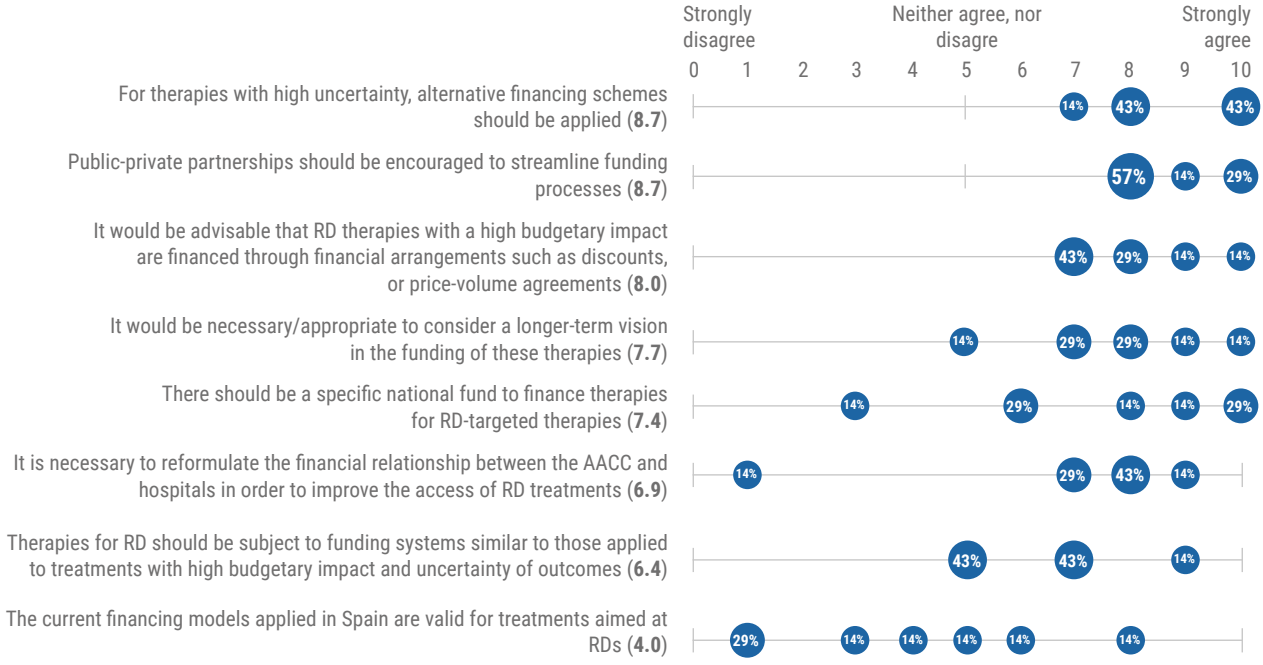

When asked about specific aspects of funding and access to RD therapies, most WG3 experts felt that, if there was a threshold of acceptability to pay, it would be reasonable for it to be different for a RD than for a prevalent disease. They also agreed that there should be differences in funding for both types of therapies. On the other hand, they did not believe that TPRs are more useful for deciding price and funding in RDs than for prevalent diseases, or that the new methodology covers the specific caseload in RDs. Here, it should be noted that the diagnostic questions were asked before they were made aware of the new TPR plan. There was less consensus on whether the current funding of RD-targeted therapies favours patient access to these therapies (Figure 28).

**FIGURE 28. RATE FROM 0 TO 10 YOUR LEVEL OF AGREEMENT WITH THE FOLLOWING POINTS REGARDING FUNDING AND ACCESS TO RD THERAPIES (0 BEING THE MINIMUM AND 10 THE MAXIMUM) (N=7)**



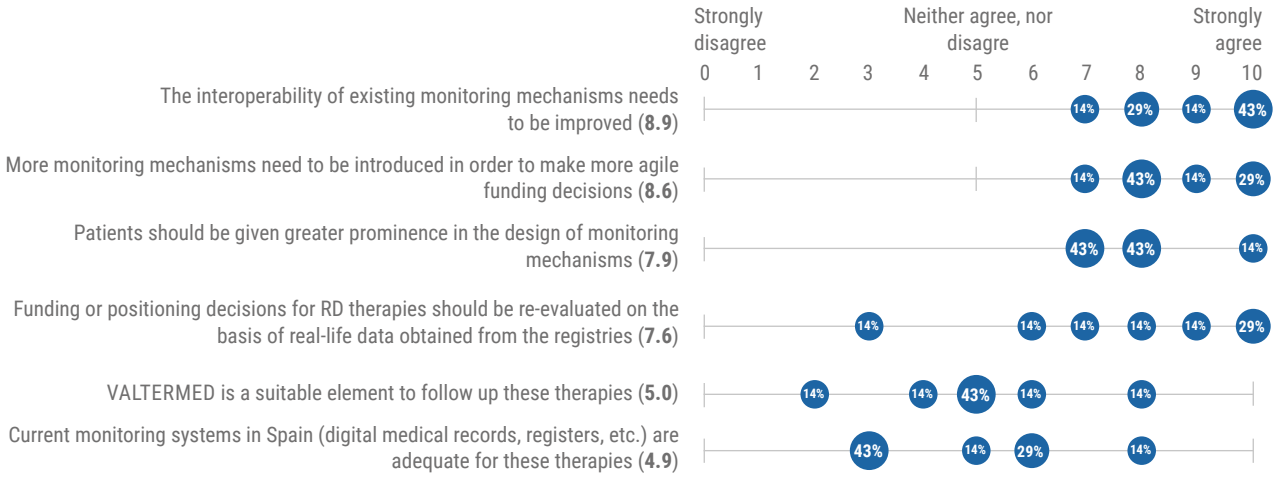

For their part, WG3 experts agreed that alternative financing schemes should generally be applied when there is high uncertainty about the therapy (8.7 out of 10). They also advocated encouraging public-private partnerships to speed up processes (8.7). On the other hand, there was less consensus on the creation of a specific national fund for these therapies and, above all, on whether the financing models applied in Spain are valid for treatments aimed at RDs, with the majority of experts disagreeing with this assertion (Figure 29).

**FIGURE 29. RATE FROM 0 TO 10 YOUR LEVEL OF AGREEMENT WITH THE FOLLOWING POINTS REGARDING THE FUNDING FORMULAS FOR THERAPIES FOR RDs (0 BEING THE MINIMUM AND 10 THE MAXIMUM) (N=7)**



Regarding the monitoring of these therapies, most WG3 experts believed that there is a need to improve the interoperability of existing monitoring mechanisms, as well as to introduce more monitoring mechanisms to streamline funding decisions. In turn, WG3 members believed that funding or positioning decisions should be re-evaluated on the basis of real-life data obtained from registries. On the other hand, and although there was some dispersion in opinions, it seems that they did not believe that the current monitoring systems in Spain are adequate for therapies targeting RD, or that VALTERMED is a very suitable element to monitor these therapies (Figure 30).

**FIGURE 30. RATE FROM 0 TO 10 YOUR DEGREE OF AGREEMENT WITH THE FOLLOWING POINTS REGARDING THE MONITORING OF RD THERAPIES IN SPAIN (0 BEING THE MINIMUM AND 10 THE MAXIMUM) (N=7)**




It should be noted that, once this diagnosis had been drawn up, WG 4 was set up, with a more political profile and a different methodological approach to the rest. This WG focused on debating and reflecting on the implementation of a new model for financing and access to RD therapies in Spain, based on the recommendations made throughout the project up to that point. For this reason, the members of WG4 did not make an explicit diagnosis of the initial situation that we can summarise in this section.

### 4.4. FEATURE HEADLINES

At the end of each working meeting, the experts provided a closing headline that summarised the most salient elements for them.

- "This strategic think tank on financing and access proposes improvements for equitable access to RD therapies, such as the promotion of stable and transparent structures to ensure access".
- "A streamlined mechanism must be put in place to accommodate the tools developed for access and maintenance of treatment".
- "An agreement between all stakeholders is needed to improve patients' access to therapies".
- "Access to medicines must be guaranteed and it is mainly due to a twofold problem: the lack of sufficient and adequate evidence for evaluation, as well as the budgetary pressure that often comes with medicines considered innovative, both of which apply

to ODs".

- "Access and funding of therapies for RDs requires measures at a specific level that all diseases require at a general level. The reality is that there are delays which, by affecting access and funding for all medicines, also affect those for RDs. If the first ones are improved, which is absolutely necessary, the second ones will also be improved".
- "This multidisciplinary committee aims to improve the accessibility of treatment for patients with RD and to let them know that they and their families are involved in the decision-making process".
- "There is still a long way to go to solve the problems faced by RD patients and their families, but there is also a lot of hope".
- "The patient and the patient's family must be at the centre of all actions, not only from a healthcare perspective, but also socio-sanitary".
- "We must give visibility to patients with RDs despite the fact that many of them do not have a specific and/or effective treatment yet. Despite scientific advances, we still have a long way to go".
- "The patient is the true protagonist of the care process, and no one knows this better than RD patients, who are particularly active in calling for an awareness of their situation and their needs. An awareness that refers to the institutions, the Administration, the healthcare system and, in general, to all citizens".
- "We must resolve funding decisions in a timely manner to achieve equitable access to medicines for the treatment of RDs".
- "We need better-trained professionals and better-informed patients, with better coordination and information flow in the treatment of RDs".
- "A good governance model for these databases must be ensured".
- "Before collecting data in real life, it must be analysed what data should be collected and what it will be used for, taking into account the opportunity cost of collecting it, both in terms of staff and time".
- "These databases should be standardised so that they can collect information from different hospitals, for the sake of efficiency in data entry".
- "Within the regions themselves, data should be shared between the different levels of health care (primary, inpatient, etc.)".
- "The inclusion of data in the register must be agile, and it is therefore proposed that there should be a data manager in each centre to support the work of the clinician. These data managers should be coordinated at the level of the different centres and the Autonomous Community".
- "The databases should contain clinical data, as well as information reported directly by patients".
- "Databases should collect information on direct and indirect costs, quality of life and

productivity measures of both patients and their carers, PROMs and patient-reported experiences (PREMs). Unlike at present, these data should be collected systematically or on an ad hoc basis in hospitals, through new questionnaires".

- "The body in charge of compiling these registers must involve patients".
- "The registries could be used for the re-evaluation of therapies in terms of positioning and price renegotiation. In addition, experts suggest that there should be a set timeframe for re-evaluation. Registries could allow payment-by-results models to be established".
- "The foundations must be suitable for use with Big Data (structured information)".
- "Price, financing and effective access, the unresolved issues for RD therapies to reach patients".
- "Fair prices are needed for the ODs".
- "When we talk about pricing, it should be done for the value it brings in terms of pharmacological value, adverse effects and quality of life, with the understanding that this value produces savings for society".
- "Financing ODs is a challenge for everyone (system and society as a whole), but it is a feasible challenge. All actors are committed to making this a successful enterprise".
- "New financing models are needed for RDs".
- "The pharmaceutical strategy is to reach new price agreements, being careful with payment by value as it depends on the chosen comparators. All of this in order to maintain the sustainability of the system".
- "We need to change the current model of public-private collaboration in RDs, finding a new formula for collaboration between both parties, beyond financing, and with a greater commitment from industry".
- "The best plan to support RDs is to seek new formulas for equity, transparency, financing, and participation above all".
- "RDs require special methods, but at the same time deserve the same level of efficacy, quality evidence and excellence as prevalent diseases".
- "Collaboration and creativity for equity. A different model is needed, changing the lens and doing it in a collaborative way to achieve equitable access to treatment".
- "We must achieve national agreements on all fundamental elements, such as research in European networks, tax incentives and early diagnosis, while ensuring equitable access to therapies".
- "Political will is essential at the national level, but capacity is limited, resources are finite and the budgetary pressure for innovative medicines is very high. This is not to say that protocols should be improved and equitable access guaranteed in every corner of the country, but a major European agreement is needed to achieve equity and accessibility to these types of therapies".

- "We have to look with a strategic and high vision, to do things as good as possible, always within the EU framework, sometimes leading and sometimes replicating good practices in our environment".
- "Excellence in rarity. We must seek excellence in RDs by treating them differently than other pathologies. It is necessary to unify what is dispersed. What is connected, make it work, and unite Spain with Europe".
- "Cooperate to move forward, share to move forward and use centralised purchasing of medicines as a negotiating tool with pharmaceutical companies to reduce the price of ODs".
- "Early and expeditious diagnosis, active policies in favour of patients and their families and a policy to promote research and investment in ODs".

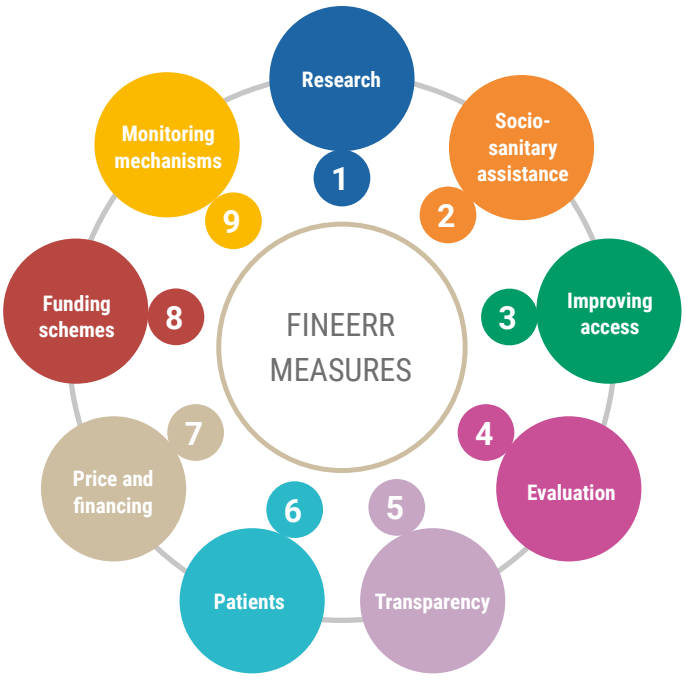
# 5

# RECOMMENDATIONS

The initial situation was reflected upon and discussed in the working group sessions based on the previous diagnosis, and multiple measures for action in the areas in question were proposed and debated, based, where appropriate, on the actions that had emerged in the previous groups. Finally, the half a hundred measures proposed by the different experts were pooled so that all the experts could be familiar with them and evaluate them in terms of relevance and feasibility of implementation, thus enabling conclusions to be reached.

The 50 measures that have emerged throughout the project have been grouped into nine action areas: research, social and health care, improving access, evaluation, transparency, patients, price and financing, financing formulas and monitoring mechanisms. These measures are outlined below (Figure 31). They are accompanied by the average score given by experts to each of them in terms of relevance (out of 10 points) and, if applicable, feasibility (percentage of experts considering the measure highly feasible). It should be recalled that only the perceived feasibility of the most relevant 25 recommendations was discussed by the experts, so not all actions have this information on their potential ease of implementation.

**FIGURE 31. ACTION AREAS OF THE MEASURES PROPOSED BY THE FINEERR WGs**



## ÁREA 1: RESEARCH

### 1. REFORMULATE EUROPEAN R&D INCENTIVES

Twenty years after its creation, the system of incentives for RD research, as set out in the European Parliament's Regulation N° 141/2000, is in need of reformulation. The required evaluation has already begun at European level.

**RELEVANCE**

**7.55**

Since the implementation of the European incentives for research in RDs, important changes have taken place in the field of diagnostics and therapies, and it is therefore considered necessary to review and reformulate the incentive system. The legislation needs to be reviewed, identifying flaws and misapplications in its content, and aligning its objectives with current research and market realities. This is particularly necessary for cases where no therapeutic options are available, for serious life-threatening diseases or for diseases of very low prevalence. The review also calls for the COMP to be more than an advisory body, and for early dialogue between stakeholders, in a framework that encourages the collection and unification of evidence following the commercialisation of the ODs.

### 2. ENHANCE RD RESEARCH

The framework of research incentives offered by member states should be further structured. It is advocated that research into the development of new molecules, compounds and advanced therapies (with drug repositioning) should be further enhanced, and that research centres should be encouraged to carry out research into RD-targeted therapies by allocating more funding to improve and motivate ODs research.

**RELEVANCE**

**8.06**

It is essential to boost RD research, with more funding, as well as to create a collaborative research framework where academia, industry, hospitals and research agencies work in coordination. Recognition at European level makes the need for research funding much more visible.

**FEASIBILITY**

**57.5%**

Although some experts believe that the COVID-19 pandemic has caused this type of research to be sidelined, most believe that one of the main consequences of the post-COVID-19 pandemic has been that society has been able to appreciate the importance of pharmaceutical research. We find ourselves in a social context that is favourable to deepening powerful and well-defined research strategies. However, many experts believe that this measure is impractical, difficult to introduce among researchers, complex to coordinate and unlikely to generate the desired results. Moreover, they argue that incentives' policies on RD research should be supranational to ensure their effectiveness.

### **3.** TAX INCENTIVES FOR R&D IN RARE DISEASES

These incentives should be applied from the earliest stages of research and not only when research is already advanced. They could be implemented through corporate tax deductions for companies reaching certain research milestones.

**RELEVANCE**

**7.13**

In the case of strategic medicines under research or in production (e.g. essential, but also ODs), companies could be awarded an additional score to the usual PROFARMA score. Furthermore, it would be interesting if the if the incentives' programmes are agreed by the EU, within the framework of a strategic development plan, protected by the Union. In any case, an evaluation would be needed to determine the desirable increase in tax incentives.

### **4.** IMPROVE THE ADMINISTRATIVE AND LEGAL CONDITIONS FOR CLINICAL TRIALS

Insurance barriers, legal and ethical constraints and permissions required for clinical trials in academic institutions, whether in single or multi-centre trials, should be reduced. It is also proposed to encourage the pharmaceutical industry's interest in supporting academic RD research centres by reducing administrative and legal procedures.

**RELEVANCE**

**7.03**

Although the level of clinical trials with ODs in Spain is high compared to other EU countries, it is important to lighten the bureaucratic and administrative aspects to make research more agile and dynamic, avoiding an investment of time that takes away from tasks inherent to the research process. It would be important to encourage interest (in general, not just from "big pharma") in developing trials for ODs. Some experts question the reduction of ethical constrains. Other experts mention the a priori challenge of balancing agility with legal certainty for the sponsor, patient and researcher.

### **5.** MECHANISMS FOR RAPID RECRUITMENT OF PATIENTS FOR CLINICAL TRIALS

The good practices used in some hospitals on rapid patient recruitment for clinical trials should be used and applied throughout the territory, which would make Spain a major centre of RD research in Europe.

**RELEVANCE**

**7.97**

Despite the existence of some platforms that follow all good clinical and data confidentiality practices in order to have a registry of patients with RDs who may be future candidates for clinical trials (e.g. ENROLL HD), it is often very difficult to identify, in Spain, a global figure for some diseases. Therefore, this measure is considered essential to better screen candidate patients and to obtain the necessary number of patients for CTs. For some, the mechanism should be linked to a system of expert centres certification, which do not always coincide with the CSUR.

FEASIBILITY

80.0%

Spain already has significant experience in this area, which would facilitate the development of this initiative. Although the descentralized healthcare system and the dispersion between AACC is an obstacle to this line of action, the feasibility of this measure could be achieved in different ways: by involving patient organisations in recruitment, in the design of the CTs protocols and in the selection of the hospitals where they are to be carried out; by promoting more coordinated collaboration between the different AACC and intensifying the collaboration between clinical centres, regional authorities and research centres, which would facilitate and speed up patient recruitment; and, finally, by encouraging networking in the NHS and the digitalisation of clinical records, as this would facilitate the identification of affected individuals and coordination with research centres. There are very interesting experiences that could be exportable.

### **6.** ENHANCE PUBLIC-PRIVATE COLLABORATION IN RESEARCH ON MEDICINES FOR RARE DISEASES

It is proposed to further promote co-development models in which the government would be involved from the early stages in the design of clinical trials (similar to the current development of vaccines against COVID-19).

RELEVANCE

8.26

Enhancing public-private collaboration to involve all relevant stakeholders in the R&D process would improve predictability and optimisation of resources, minimising biases due to commercial interest. Furthermore, the involvement of the administration and academia in the inclusion criteria of clinical trials would minimise the risk of focusing the final indication of the drug on a very specific segment of patients.

FEASIBILITY

75.0%

Public-private collaboration in research is a feasible measure when apolitical will exists, and the example of COVID-19 is a paradigmatic case. The current situation (in a context of pandemic) can offer great opportunities and allow this collaboration in RDs, which should aspire to be international, and which could be included in a future update of the Spanish RD Strategy and be nourished by European resources from Horizon Europe. The new public sector procurement law contemplates and protects it. In any case, all the agents involved must do their part, and early dialogue and a regulatory framework are needed to establish transparency criteria and a balanced distribution of benefits. Some obstacles to this are the administrative mechanisms of the administration and the lack of resources and personnel in the public system to undertake this task.

### **7.** SHARING ACCESS TO NEGLECTED INDUSTRY RESEARCH

In order to encourage access to molecules with little commercial interest, a system in which industry shares research on molecules already under investigation with academic centres is proposed, provided that these molecules are not in the pipeline of industry and under certain conditions of research and collaboration between both parties.

**RELEVANCE**

**7.23**

It is very interesting to consider the path that could be followed in this area, as it seems that interest is usually focused on high-cost medicines. To this end, it would be appropriate to identify successful experiences with this type of assignment in order to encourage agreements and thus promote access to medicines with little commercial interest. In any case, it would be necessary to analyse their regulatory possibility.

## **ÁREA 2:** SOCIO-HEALTH CARE

### **8.** DIAGNOSTIC HARMONISATION BETWEEN AACC

It is proposed to design and coordinate the implementation of patient referral procedures at national level between the centres authorised for this purpose. It is also recommended to implement a system of equal screening between the different AACC, both with neonatal screening in the first instance and with population-based screening in the foreseeable future. This screening would be selective in nature, in those pathologies where it has been demonstrated that early treatment can change the course of the disease through early detection. This harmonisation of screening should take place not only at national but also at European level. A more coherent framework for neonatal screening and detection is needed to allow earlier diagnosis.

**RELEVANCE**

**8.47**

It is important that many aspects of care are harmonised at national level, to promote equity in the provision of services and resources, especially for diseases where therapy is much more effective in pre-symptomatic individuals. Some point out that harmonised screening between AACC makes complete sense and should be promoted, admitting that it is not all about technological facilities for screening, but that the follow-up of detected cases presents differences that would require clear referral procedures. On the other hand, some experts point out that, rather than referring patients, samples should be referred, promoting the dissemination of knowledge between professionals, creating a diagnostic programme and increasing the neonatal screening programme as an opportunity for access to treatment, early diagnosis for prevention, information, registration and follow-up research.

**FEASIBILITY**

**52.5%**

This is a difficult measure to achieve in the short to medium term, given the territorial organisation of the State (with AACC with their own competences in health matters) and the existence of so many agents involved, which does not favour the adaptation of joint and common strategies. However, in the long term it could be a feasible strategy if progress is made towards a more egalitarian diagnostic and screening system among the AACC, with the involvement of scientific societies for training in the detection of RDs and the ministry playing a coordinating role. Political will is needed. Feasibility would increase if there were agreement at national level and in advance, that the only procedures would be those adopted and updated by a commission of experts, with no exceptions in the AACC. Not only should diagnostic procedures be improved, but it is also crucial to speed up the prescription and performance of diagnostic tests as much as possible. It would be important to focus on molecular diagnostics and personalised precision medicine.

### 9. IMPROVE REFERRAL PROCESSES WITHIN AND OUTSIDE CENTRES, SERVICES AND REFERRAL UNITS (CSUR)

Administrative procedures that delay referral should be reduced. In addition, information to both patients and professionals should be increased in order to reduce referral times to the minimum.

**RELEVANCE**

**8.47**

Reorganisation and simplification of referral processes is central to speed up treatment and ensure early access for patients to a reference centre. Moreover, all patients have the right to be treated equally, regardless of their geographical location, and this measure would allow progress in territorial equity. The use of telematics could reorder and simplify some of the procedures. The system should be properly linked to the European Network of Reference Centres.

**FEASIBILITY**

**77.5%**

It is a feasible goal with potential for improvement in terms of quality and equity. According to some experts, this is a strategic and administrative problem, so that, if there is the will, administrative procedures should be streamlined so that they do not slow down the referrals made by specialists. On the other hand, others indicate that the problems of referral are not so much in the processes, but in the funding and the interest in keeping more complex patients, which is necessary political agreements beyond purely health-related issues.

### 10. IMPROVING THE CONCESSIONS AND FUNDING OF CSUR

It would be necessary to determine an appropriate CSUR policy that is not based on defining evaluation criteria. It would also be desirable to have a plan for the distribution and definition of the needs to be met by the CSURs, including the designation of new centres on a competitive basis and not so much at the proposal of the AACC, to which a certain territorial equality factor should be added. This would apply both to newly created CSURs and to the designation of new CSUR categories.

**RELEVANCE**

**8.23**

Some experts considered that the quality of everything related to CSUR should be streamlined and improved, both for existing and newly created CSUR, redefining both the concession and the financing of the centres. The territorial equality factor cannot be a criterion in itself for pathologies requiring a high degree of specialisation that cannot be improvised. It is necessary to reduce the existing territorial inequality between AACC. On the other hand, others believe it is inappropriate to expect the AACC not to give their approval and/or propose that services under their competence and responsibility should be a reference for the rest of the health system.

**FEASIBILITY**

**32.5%**

Although this is an important measure, it is not very feasible and has been requested for years without success. On the one hand, it is difficult to apply because of the decentralisation of competences between the AACC in Spain; and, on the other hand, because it would require funding and resources for them, which would be difficult to achieve given the current political framework.

### 11. INCREASED INCORPORATION OF CSUR INTO EUROPEAN NETWORKS

It is proposed to achieve a greater incorporation of the CSUR in the European Reference Networks (ERN), to take advantage of the knowledge generated in this network and to stimulate a better treatment in the field of RDs, where the dispersion and the small number of cases make health care more difficult.

**RELEVANCE**

**8.06**

Some experts see this as a priority. Joining the ERNs would be of great benefit to people with RD, as it would help to ensure that CSURs have up-to-date and comprehensive information on diagnosis, care and treatment, and would also facilitate contact between European experts. For some, it is more important to ensure presence in the European Networks, i.e. that qualified units are part of the ERN System and there is a network that allows access to the knowledge and/or management of patients from all hospitals through the Network's member Centres and Units. However, some people think that the concept of CSURs differs from the ERNs concept, as there are CSURs that do not focus on RDs, or that focus on a procedure rather than a disease or group of diseases.

**FEASIBILITY**

**72.5%**

Many experts agree that this measure is essential and quite feasible, and it could be an ideal moment to define a strategy for the European integration of these reference networks. However, this requires a long process and will depend on the willingness and resources of the CSURs to adapt to the regulations and requirements of the ERNs. The CSUR designation pathway does not necessarily correspond to the concept described in the ERNs, and represents a slow administrative procedure that has been limiting in the initial phases of deployment. It requires a huge effort and a long way to make it feasible. The European Commission's regular calls for new service providers are an opportunity in this respect, although national solutions should be searched if the new European EU4Health programme does not solve the problem.

### 12. IMPROVE THE TRAINING OF HEALTHCARE PROFESSIONALS IN RARE DISEASES

In order to improve training, it is proposed to include specific subjects on RDs in Medicine and Nursing degrees. Likewise, it is advocated to promote a greater presence of RDs in specialised health training programmes of health professionals as an attempt to link these diseases to the development of their professional careers.

**RELEVANCE**

**7.69**

The inclusion of subjects on RDs is important and linking it to career development would stimulate the interest of professionals, increasing their knowledge in this type of disease. However, RDs encompass a considerable number of different pathologies, so some experts point out that it is not an easy task to design specific subjects in this respect, unless training is oriented towards the (non-clinical) management of these diseases. Other people think that training should focus on the pathologies, their approach and treatment, including their legislative aspects.

### 13. ESTABLISH STANDARDISED RULES OF SOCIO-HEALTH CARE AT NATIONAL LEVEL, BEYOND SPECIFIC TREATMENTS

It is proposed to harmonise, at national level, the standard of care, rehabilitation, psychological and other social and health care that RD patients need beyond the strictly pharmacological treatment. All care should be harmonised in the pursuit of excellence in the patient's care.

**RELEVANCE**

**8.44**

The integration of general and specific care for patients affected by RDs and their families is sometimes more important than specific medicines and treatments. However, there are difficulties in integrating or coordinating these elements, which often have different dependencies and do not consider certain closely interrelated aspects such as health and social care. Moreover, compliance with standards and equity in access and treatment for these patients is essential and a basic condition for the social cohesion of the NHS, to maintain the effectiveness of sophisticated (in some cases expensive) treatments and to enable comprehensive patient care. Principles of care could be created to harmonise care.

**FEASIBILITY**

**40.0%**

This is an important measure, although difficult to achieve in the short to medium term, as it involves resources and processes that are not currently included in the health services portfolio, i.e. it exceeds the capacity of the health system itself. The need for different human resources (social work, physiotherapy, psychology), along with the decentralisation of competences, makes such harmonisation complicated. Moreover, it would require an enormous organisational and resourcing effort. However, some experts argue for its feasibility in the medium term, as they consider that stakeholders (rehabilitators, social workers, psychologists, patients' associations, etc.) can reach an agreement at national level to standardise social and health care. Others call for a greater role for patient associations and scientific societies.

## ÁREA 3: IMPROVING ACCESS

### 14. GREATER COLLABORATION BETWEEN EMA AND FDA IN THE AREA OF ORPHAN DRUGS

To improve access times, there should be closer collaboration between the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA), in which the approval of RD-targeted therapies is commonly done.

**RELEVANCE**

**6.87**

For some experts, this measure, while desirable and possible, has limitations and is not a priority, since the difficulties of the ODs appear after the evaluation procedure and this closer collaboration could generate the opposite effect and lengthen access times. Moreover, decisions in an environment so marked by contextual criteria and with the degree of uncertainty involved in RDs must take into account the variability of healthcare models and financing systems.

### **15.** ESTABLISH EU CENTRALISED PURCHASING AGREEMENTS FOR ORPHAN DRUGS

These centralised purchasing agreements would be supported by the european legislation approved by the European Commission in April 2014. This legislation allows to jointly procuring medical countermeasures for different categories of cross-border health threats, such as vaccines, antivirals and other treatments, and guarantee more equitable access and greater security of supply, in addition to more balanced prices for countries.

**RELEVANCE**

**7.59**

While this may seem like an important step, some experts are doubtful that such practices will improve effective access in some countries and may interfere with national health competences. They argue that centralised purchasing would only be possible in cases of public health problems (e.g. as it has been the case as a consequence of the pandemic and COVID-19 vaccines) and they do not think that it is the best solution at a general level to ensure access and balanced prices. They also point out that the economic impacts and burdens of RDs on health systems are not comparable across European countries and that decisions cannot be separated from budgetary management. However, they also recognise that the structure for such agreements is already in place and that collaborations for some medicines between groups of countries where patients are dispersed could have positive effects. On the other hand, some experts clarify that centralised procurement could also be, depending on the case, at regional and/or national level. Hospital-by-hospital procurement may lead to different criteria and inequalities to the detriment of patients.

### **16.** NATIONAL POLITICAL AGREEMENT

Due to the far-reaching nature of the recommendations, and in order to promote access in the field of RDs, a national agreement between all political parties would be desirable, starting with those measures with greatest consensus. There is also a strong need for agreement among all stakeholders to improve patient access to therapies.

**RELEVANCE**

**8.03**

Decisions on access to therapies for RDs are extremely complex, which is why some of the experts recommend to reach a national political agreement that provides greater transparency, objectifies decision-making and facilitates the consideration of rationality, equity and justice criteria, in order to achieve the greatest possible consensus at national and international level to avoid dispersion (in the expected absence of agreement, transnational recommendations should prevail). The importance of establishing an ethical pact with media that, while guaranteeing the fundamental right to information, avoids the exposure of vulnerable groups privacy for the sake of information impact, especially in the context of complex access negotiations. On the other hand, some experts state the importance of political support and leadership in favour of access in RDs, but do not believe that a national pact is necessary to make these changes.

FEASIBILITY

25.0%

Despite its relevance, this is the least feasible measure, with the support of only 25% of experts. Most agree that, with the current political framework, it is very difficult to reach a global political agreement beyond general aspects on the importance of access to RD therapies. Some believe that access decisions should be technical and not political, based on guarantees of quality, efficacy, safety and sustainability, under criteria of beneficence, distributive justice and equity in access, since politics incorporates elements of decision making that may compromise some of the basic guarantees and criteria. Conversely, others consider that an institutional agreement between administrations (central and regional) would be more feasible.

### **17.** CALL FOR EFFECTIVE COMPLIANCE WITH ARTICLE 91 OF LEGISLATIVE ROYAL DECREE 1/2015 ON TERRITORIAL EQUALITY AND COORDINATION

In order to promote equity in access, we urge compliance with the provisions of article 91 of RD 1/2015, which approves the Law on Guarantees and Rational Use of Medicines, and recognises the right of all citizens to obtain medicines under equal conditions throughout the NHS, without prejudice to measures aimed at rationalising the prescription and use of medicines that the AACC may adopt in the exercise of their competences.

RELEVANCE

7.68

It is important to remember this legal precept in terms of equitable access, as it must be made effective through homogeneous management and the reduction of variability in clinical practice. Moreover, this measure should not only apply to medicines, but to health and social care as a whole, as basic determinants of people's health. In any case, some experts point out that the Spanish state model is decentralised and that, therefore, unless it changes radically, the decisions to prioritise services present in all the AACC must be local.

### **18.** CREATION OF A CENTRALISED ENTITY IN RARE DIEASES

The creation of a centralised entity is proposed, with its own budget and an advisory committee to make decisions on the authorisation of treatments for RD or ultra-RDs patients at a national level, similar to the model used for transplants or CAR-Ts.

RELEVANCE

7.23

There is a significant agreement that the creation of this centralised entity could be of interest to guarantee equity in access to therapies. However, several experts question its suitability in the decentralised context of the Spanish health system, perhaps with some exceptions for ultra-rare drugs for which the provision cannot be offered in all AACC. Others reject that it should have its own budget. Neither the economic impact nor the burden of RDs on health budgets is comparable across the AACC, and they could generate inequities in other pathologies causing more obstacles and delays.

### **19.** SPECIFIC PROCEDURE TO ACCESS RD-TARGETED THERAPIES

A specific procedure for early access to these therapies is advocated, guaranteeing a faster (fast-track) pathway to potentially (highly) innovative therapies and for diseases with significant unmet needs (not necessarily for all ODs). This pathway should allow the possibility of repositioning and assessing the best therapeutic options. In turn, there should be a consensus with representatives of all actors involved.

**RELEVANCE**

**7.84**

The implementation of this measure would speed up the action of different agencies and committees. This is often complicated by different points of view (health, social, industrial, economic, patient, researcher, health professional, manager, etc.). However, there are models in other countries that could be followed or adapted. On the other hand, there are those who consider that these mechanisms already exist and that if they are not applied it is because the circumstances described above do not exist. Some warn that sometimes disproportionate expectations are generated, confusing the great medical need with the value provided by the product, and there is pressure to grant early access that does not respond to rationality criteria. Others also highlight that this process should not slow down access procedures for other innovative medicines.

**FEASIBILITY**

**50.0%**

There are two different opinions on this issue. 50% of experts consider this measure feasible if there is political will. Indeed, they argue that such an access procedure already exists in special situations and there are examples in other countries. However, it is likely that more human and financial resources - possibly to the AEMPS - would be needed to make it feasible. The other 50% of experts belive that, despite being an important objective, its feasibility is doubtful, given the current composition of the commissions, the complexity of making it operational and the fact that Spain's administrations are not prepared for such an innovative objective.

### **20.** CHANGING ADMINISTRATIVE SILENCE FROM NEGATIVE TO POSITIVE

Some experts propose changing the concept of the administration's negative silence, so that if an express resolution of non-financing is not issued within the established timeframe, the medicine is by default incorporated into public financing (positive silence). This could be articulated through a resolution of the Directorate General for the Basic Portfolio of Services of the NHS and Pharmacy or the competent authority, establishing greater transparency and a closed timeframe.

**RELEVANCE**

**6.00**

For some experts, this measure would increase the rigour of the procedure, the motivation of the funding, and would improve the availability of medicines and access times. However, many others consider that authorisation procedures provide guarantees of rationality in the use of public resources, and that under no circumstances can they be bypassed by positive silence procedures that only benefit marketers, and which can lead to abusive negotiating positions that are unfavourable

to the interests of the population as a whole, as well as creating legal uncertainty. Others point out that this measure would not be functional in practice, so it would be more advisable to work on speeding up the procedure and creating rigidity in meeting deadlines.

### **21.** CREATION OF A MATRIX TO ENSURE COMPLIANCE WITH TIME LIMITS

In order to identify the responsibility of both the industry and the administration for the delay of deadlines, a time matrix could be created to explicit the maximum time for each process for all actors involved.

**RELEVANCE**

**7.59**

Part of the opinions are favourable, as they consider that this measure would help to meet the stipulated deadlines and would be an important tool for monitoring the dossiers in the administration, which would help to know at what stage the medicines are at and how they are evolving. However, it could have the opposite effect and reduce the speed of the procedure. In addition, it is often difficult to identify who is responsible for the delay.

### **22.** PENALIZE LACK OF DILIGENCE IN ACCESS BY THE AACC

In order to promote equity and agility among the different AACC, some experts propose establishing a series of indicators for patients' real access to these therapies, so that patient access can be monitored. They also suggest to penalise those AACC that do not meet the agreed minimum indicators, preventing or limiting their access to the funds in the complementary portfolio.

**RELEVANCE**

**6.42**

This measure is strongly questioned by some experts, who argue that penalising the AACC is not the most appropriate incentive to speed up timescales, but that the measure should focus more on generating a legal framework that guarantees compliance with the publication of indicators that favour equity in patient access. Preventing or limiting the AACC access to the funds in the complementary portfolio could be detrimental to patients. On the other hand, comparison and benchmarking exercises can be very useful if they are well conducted and the purpose for which they are carried out is well defined.

### **23.** BETTER ACCESS IN SPECIAL SITUATIONS, CREATING SPECIFIC CENTRALISED COMMITTEES

It is recommended to consolidate a consensus among the AACC on the criteria for access to RD therapies in special situations, with representation of all actors involved. This regulation would be carried out at national level, avoiding subsequent readjustments at an autonomous community level. Legislation should be improved so that access for compassionate use is not delayed, establishing general access criteria in the interest of equity.

RELEVANCE

7.69

Legislation already exists to regulate access to medicines in special situations, focusing in situations where there are no therapeutic alternatives for specific cases of great medical urgency and severity. Hence, the measure should be aimed at reformulation (i.e. reviewing) this legislation to improve and reorder the conditions and procedures for access to therapies in this way, and not so much at creating more committees. Therefore, in order to ensure cohesion, the conditions for early access in special situations should be legislated, standardised and include not only centralised assessment, but also clear criteria on in which situations it is acceptable and in which it is not justified. It should also specify the applicable free of charge, or type of financial compensation, that should prevent abuse by pharmaceutical companies of the costs of early access, and also prevent conditioning subsequent price and reimbursement negotiations.

## **AREA 4:** EVALUATION

### **24.** RECONSIDERATION BY THE EMA OF THE EVIDENCE REQUIREMENTS FOR THE AUTHORISATION OF ORPHAN DRUGS

The EMA should tighten, or at least make explicit, the conditional approval which, although they have favoured access to new RD therapies, have led to the commercialization of drugs with poor efficacy that are difficult to withdraw from market. Other systems that allow to continue product research should be searched, without granting commercialization authorisations.

RELEVANCE

7.09

Some experts argue that conditional authorisation procedures that are not subsequently reviewed are a distorting factor in funding decisions that should be reconsidered. The difficulty with these medicines is that access is very limited (precisely because of their low scientific evidence), which generates high expectations in patients, while access is ineffective, causing enormous frustration. In this respect, there should be greater collaboration between the EMA and national evaluation agencies and payers.

### **25.** MINIMISE THE IMPACT OF COST-EFFECTIVENESS ANALYSIS IN THE DECISION TO FUND THESE MEDICINES

Economic evaluation is one of the criteria for public funding, but there are others, such as social and humanistic criteria, which it would be desirable to incorporate in order to modulate the final pricing decision. Thus, in RDs, the cost-effectiveness criterion should weigh less than in other prevalent pathologies. In the TPRs, it is proposed to include these additional social criteria in the specific node for advanced therapies and non-oncological RDs, so that the decision is not based solely on the result of the cost-effectiveness analysis. Furthermore, it is important that in this node the economic analyses take into account the direct (health and non-health) and indirect costs associated with the intervention, so it is possible to capture not only the impact on patients, but also on their carers (formal and informal) in terms of quality of life and loss of productivity.

RELEVANCE

7.44

Some experts believe that efficiency should be incorporated into decision-making as one criterion, although on certain occasions, efficiency should take second or third place, since in this type of drug cost-effectiveness analyses lose their original meaning and it is important to consider all costs and all relevant benefits for society as a whole. On the other hand, other experts consider that economic evaluation should not be adapted to any specific pathology and that, although for RDs there is less likelihood of fulfilling the efficiency criterion, if they demonstrate health gains this probability decreases, as for other pathologies.

### **26.** POWERFUL STATISTICAL ANALYSIS OF THE EVALUATIONS AND A SECTION ON THE VALUE OF THE INFORMATION

In order to adequately manage the clinical uncertainty associated with RDs and the clinical effect of treatment, it would be necessary to combine the economic evaluations with a robust probabilistic analysis. A section on the value of information could also be included in the value dossier provided by the pharmaceutical sponsor.

RELEVANCE

7.47

Some experts believe that for a correct assessment it would be necessary to visualise and quantify the absence of information and uncertainty as the absence of value. On the other hand, others consider this measure to be of little relevance, some because they consider that a powerful statistical analysis is already carried out and others because they believe that social and humanistic aspects should be taken into account over complex statistical analyses that hardly help decision-making.

### **27.** DYNAMIC CLINICAL AND ECONOMIC RE-ASSESSMENT

Dynamic re-assessment of innovations should be promoted, with new information collected, which is particularly relevant when uncertainty is high. The type of information to be collected should be designed according to the type of uncertainty (clinical or economic) involved, as well as the most appropriate results-based financing model. To this end, appropriate collection of information on benefits, safety, direct and indirect costs and budgetary impact should be promoted.

RELEVANCE

8.47

It is important to encourage continuous, dynamic and rapid evaluation as evidence is generated from new information gathered, but medicines should be selected for detailed follow-up and outcome evaluation (many ODs would be good candidates for this, especially those with performance-based funding schemes).

**FEASIBILITY**

**47.5%**

More than half of the experts consider that this measure is not very feasible: the system is not designed or prepared for it, and it requires coordination at a very granular level which is complex, unless it is linked to management elements that inevitably require registration, so that the negotiation and financing models should be changed beforehand and the companies must allow a change in the financing conditions. On the other hand, 47.5% refer to the fact that it could become a feasible measure in the medium term. A complete re-evaluation protocol is a time-consuming task, but it could be developed, given that all actors are involved and specific resources are provided to carry it out. It is proposed to start with a small group of medicines and to extend this reassessment to more medicines in the medium and long term.

## **AREA 5:** TRANSPARENCY

### **28.** METHODOLOGY AND DEADLINES FOR EVALUATION AND ACCESS

It is proposed to improve the transparency of the regional and hospital pharmacotherapeutic commissions in terms of evaluation times and procedures, in order to achieve a more effective access to ODs in healthcare centres.

**RELEVANCE**

**8.09**

The experts agree that it is important to implement any measure that clarifies and speeds up patients' effective access to treatment, without increasing the administrative burden, and that it is also necessary to standardise the assessment criteria and procedures between AACC as much as possible.

**FEASIBILITY**

**62.5%**

Although the descentralized healthcare system and the high dispersion among AACC is an obstacle, this is a feasible action measure. It would require, among other actions, political will and a rapid agreement between marketer and administration on fair and proportional prices.

### **29.** MANDATORY PUBLICATION OF THE THERAPEUTIC POSITIONING REPORT

Publication of the TPR should be mandatory from the moment it is carried out.

**RELEVANCE**

**8.47**

Experts agree that all TPRs should be published. According to some experts, TPRs are already public documents once they are finalised, and they represent an example of transparency.

**FEASIBILITY**

**80.0%**

Most experts consider the publication of the mandatory TPR to be feasible, as it is provided for in Law 10/2013, according to which the actions aimed at establishing the position of a medicine in the pharmaceutical provision and its comparison with other therapeutic alternatives will have a common technical scientific basis for the entire NHS and will be carried out within the framework of the TPRs of the AEMPS. These reports will be binding. In any case, a number of people claim that the TPRs are already published at the appropriate time and when they are finalised.

### 30. TRANSPARENCY IN THE QUANTIFICATION OF THE CRITERIA UNDERLINING THE FUNDING DECISION

In order to make the process more transparent, it is proposed to establish a quantification of the criteria used for the public funding of medicines included in the regulation (article 92 of RD-legislative 1/2015), so that the variables to be measured can be standardised, as well as the weighting applied to each criterion in the decision. These weightings would have margins of acceptability to adapt to heterogeneity.

**RELEVANCE**

**7.75**

Transparency in all processes is essential, also to reduce as far as possible arbitrariness in decision-making by trying to ensure that the different variables are agreed with clinical experts who are aware of the clinical sub-variants and potential complications. However, reaching consensus on the opinions of patients, funders, companies and clinicians is a difficult task in an environment of such uncertainty, and would require a great deal of effort and knowledge of each of the pathologies. In addition, the wide variety of ODs and RDs makes it difficult to introduce generalised standards of action for all cases. Some experts also warn that precise quantification of criteria may have negative consequences for access.

### 31. MORE TRANSPARENCY IN PRICING

Transparency must be improved in medicines pricing and in the contribution of public research to many of the new medicines. This transparency should be provided both by the pharmaceutical industry, by disclosing the costs of the drug research and manufacturing process, and by governments, by disclosing the price-setting elements.

**RELEVANCE**

**7.94**

The game rules must be transparent and pricing must be robust, auditable and predictable, and the system must be enforceable. Although gaps remain, transparency in the drug pricing process must be improved, in particular regarding the criteria and procedures that define precisely how the price of medicines is set, to ensure that it has been done with full guarantees. A different question is whether the final price at which the medicine is reimbursed should be known only to the health system that will use it. Most administrations consider that the dissemination of the financing price of medicines makes their price more expensive and are in favour of informing about the list price, which, according to the Law, cannot be lower than the financing price. In addition, the implications of price transparency need to be carefully analysed, both at national and global level.

**FEASIBILITY**

**40.0%**

Experts consider that, despite being a desirable objective, it is currently not very feasible, given the legal limitations and the reluctance of the industry at national and international level. However, some people think that, despite the limitations, it should be regulated. There should exist a favourable attitude of collaboration among the pharmaceutical industry, and a National Agency similar to NICE should be created. Greater transparency in research and manufacturing costs would first require a clear methodology for allocating and estimating fixed and variable costs.

## **AREA 6:** PATIENTS

### **32.** GREATER PATIENT REPRESENTATION AND INVOLVEMENT IN THE ASSESSMENT COMMITTEES

Patient's representation on medicines assessment committees would not only be of patients affected by the disease, but also of patients as a community, so that they can provide a more neutral view from the perspective of society. In addition, it is proposed that patients should be more empowered, as they are the most aware of the impact of RDs on quality of life. To this end, patient training is very important. The assessment should be carried out by independent experts, without any conflicts of interest, always taking the opinion of patients into account.

**RELEVANCE**

**8.00**

Patient empowerment and participation in decision-making processes is essential, especially in RDs, to ensure their integration as a stakeholder and to enrich perspectives, provide credibility and enhance transparency of decisions. They should be listened to and involved in the process, as the complexity of drug evaluation procedures requires a certain degree of technical knowledge and experience on their part, in order to modulate technical and emotional issues. However, some experts believe that a neutral view cannot be obtained from a patient group. Others believe that patient involvement is an interesting objective in various aspects of decision-making; but not in areas such as financing or pricing.

**FEASIBILITY**

**67.5%**

For most experts, this is a feasible goal. Patients are open to different kind of involvement ways, so it would be a question of willingness of other stakeholders. Moreover, patient education in these areas should be encouraged in order to involve them in decision-making processes with patient organisations. However, it should be borne in mind that, given the complexity of the evaluation processes, it would be desirable for them to be involved at some stages of the process if they are represented by experts in specific fields (e.g. in funding or pricing, which are not areas of their competence). It should be discussed where their involvement makes sense and where it does not.

### 33. CREATION OF A NATIONAL DIGITAL PLATFORM FOR CONSULTATION

To improve patient information, especially in the field of RDs, it is proposed to create a national digital platform to provide information about RDs and available CSURs.

**RELEVANCE**

**8.28**

Facilitating access to information on RDs for the general public is an essential task in order to facilitate early diagnosis and access to specialised resources, which is crucial to optimise the management and adaptation of patients and their families to the situation caused by the disease. However, rather than making an effort to create a national platform, some experts believe that the use of other existing national and international RD information platforms and portals should be encouraged to save resources. Others argue that this approach should be more concrete, as the improvement of the consultation structure is much more complex and current access to CSUR information is already available through SIFCO.

**FEASIBILITY**

**75.0%**

It is considered a moderately feasible action measure. The barriers would be the reluctance of the AACC to compare results and the lack of human resources for implementation and monitoring. The Orphanet database, which already includes a large part of this information, could be a good starting point to accelerate the creation and development of this platform.

### 34. VALIDATION OF SPECIFIC PROM/PREM SCALES BY PATHOLOGY

Efforts should be made to design specific and validated PROM (i.e. outcomes) and PREM (i.e. experiences) scales on RDs containing relevant and direct patient inputs, validated for our country.

**RELEVANCE**

**8.13**

Mechanisms for measuring patient-reported experiences and outcomes help in the construction of healthcare value. It is essential to develop methodologies to determine the clinical relevance of efficacy observed in clinical trials, as well as to advance in methodologies to establish the relative value of different PROMs, in different diseases. This would help to set up a context of clinical relevance between pathologies, which would be quite useful for outcome measurement and subsequent analysis. However, some experts highlight the difficulty of validating them for each individual RD or RD subgroup.

**FEASIBILITY**

**65.0%**

Some experts consider it as a feasible measure for which a major effort would be needed as it is still in an initial phase in our country and it is a tedious task that would require reinforcement of personnel and methodological validation. Resources would be needed for the development of this type of scales, as well as the involvement of patient organisations, medical experts and knowledge of international references. In addition, some consider that it should be a feasible goal even in the short term for

evaluation and reassessment to be meaningful. Others consider that, when such data are integrated into clinical registries, it is easier to identify areas for improvement in management.

### 35. PROMOTE BETTER COMMUNICATION BETWEEN HEALTHCARE PROFESSIONALS AND PATIENTS

Better two-way communication between experts in RDs and patients should be encouraged. To encourage this measure, the promotion of open days or monographic days on RDs is given as an example.

**RELEVANCE**

**8.09**

It is necessary to increase mutual knowledge, so that administrations and professionals are aware of the social, family, economic circumstances and contexts that generate diseases (the burden of disease is not only health-related). Open or monographic days are highly valued by patients and their carers.

**FEASIBILITY**

**97.5%**

This is considered the most feasible measure. Collaboration between healthcare professionals and patients is necessary and promising, and patients should be given access to congresses and scientific sessions, and information days and workshops should be organised. There is already a long way to go, and promoting greater communication only requires willpower. Others add that doctors need to be able to devote more time to their patients and to the study of rare pathologies. Reference is also made to the fact that these relationships should be developed with patient associations.

## AREA 7: PRICE AND FINANCING

### 36. HIGHLIGHTING THE SOCIAL AND HEALTH VALUE OF THE MEDICINE

The social and health value of the medicine should be taken into account, especially in rare pathologies, although it may be difficult to capture this value in pricing, in an environment where resources are finite.

**RELEVANCE**

**7.59**

It is essential that decisions on the financing and pricing of medicines are made taking into account the social and health value they bring to the population. For some, ignoring the social and health value of medicines introduces significant biases into the pricing, financing and access process. Others point out that it is difficult to visualise an articulation of this proposal.

### 37. QUANTIFY UNCERTAINTY AS A NEGATIVE VALUE IN PRICING

It is proposed to change the direction of the current price and financing model, so that the initial price set contains a discount proportional to the lack of evidence or uncertainty

regarding efficacy and safety. In contrast to the current model, in which value is taken for granted and paid in advance, despite the possible lack of effectiveness, a model is proposed in which the industry accepts financial capitulations on the understanding that they will obtain a lower price when the drug enters the market, but as evidence is generated, the administration will pay a higher price. This would require the creation of a scoreboard and an agreed timetable.

**RELEVANCE**

**7.44**

While some experts believe that the creation of a "pay per cure" reimbursement system should be the way forward for some ODs, such as those related to advanced therapies (although consensus is required to be able to increase prices in the case of positive results), others believe that penalising uncertainty would be negative and could significantly slow down patient access to these therapies. According to this, it would be important to measure the results and pay an appropriate price for the drug if it works, for which milestones, intermediate results and measurement tools that can help mitigate uncertainty should be defined.

### **38.** INTRODUCTION OF THE VARIABLE OF EXPERTISE BY THE NHS IN PRICE NEGOTIATION

In drug research, the growing participation of public funds needs to be taken into account when setting prices. The contribution made by the NHS, by providing the centres where clinical trials are carried out, as well as the knowledge of public professionals, should be valued as a discount in price/reimbursement negotiations. If the health system helps in the collection of evidence and in research, it should be rewarded with a reduction in the therapy final price.

**RELEVANCE**

**7.74**

While some experts consider this measure to be very successful, others argue that it would be ineffective and difficult to assess. The participation of public systems in the research procedure for this type of drug is already taken into account when setting the price, and they already obtain direct economic benefits and other advantages as a result, so a system of "sales" for performing the research in public centres could lead to carry out much more intensively in private centres or no longer being carried out in our country.

### **39.** ESTABLISH TARIFF MODELS BY TYPE OF RD

Due to the differential characteristics of the RDs, it is proposed to create different financing models by process or by disease (depending on clinical-care characteristics) to be applied to groups of diseases (progressive degenerative, degenerative by stages, critical illnesses) and not by individual diseases. These rate models for groups of pathologies should include comprehensive patient care beyond medication, including the social, family, educational, medical and pharmacological aspects.

RELEVANCE

7.13

For some experts, establishing tariff approximations by type can help to establish benchmarks of maximum treatment costs by comparable benefit magnitudes in types of diseases with similar functional impacts, avoiding price disproportions due to access situations at different times or in different pathologies. However, some argue that, the establishment of clusters is complicated and may lead to increased bureaucracy and discretion, and that an adaptive system would be more appropriate. Valuation models could be established for different types of medicines and diseases, also taking into account the increasing volume of ODs indicated in oncology, with specific characteristics and very significant sales volumes.

## **AREA 8:** FINANCING SCHEMES

### **40.** SYSTEMATIC APPLICATION OF FUNDING MECHANISMS FOR THESE THERAPIES

It is proposed that the marketing of any therapy for a RD should be automatically linked to a funding mechanism, such as risk-sharing agreements, health outcome-based agreements, expenditure ceilings, etc. A compliance guideline could be established as a screening process defining the use of one funding mechanism or another, based on the characteristics of the therapy. This screening would use inputs such as outcomes uncertainty and lack of identification of responders, among others.

RELEVANCE

8.25

Many experts recognise the utility of having a defined environment for the implementation of risk-sharing mechanisms, as it is important to collect, quantify and analyse the health results and costs achieved by these medicines. However, for some, such financing mechanisms, on which much progress has already been made and are being implemented, should not be limited to RDs. Some experts point out that, in the absence of uncertainty, they should not be applied systematically, but that the decision should be taken on each case separately, and that they should not lead to an overload of work without added value.

FEASIBILITY

52.5%

On the one hand, some experts consider it a feasible measure that could be achieved in the medium term, ideally at the national level, given the high costs of RD therapies. On the other hand, others consider it a difficult goal to achieve, as it is complicated to implement, and will largely depend on the pharmaceutical companies. The operational requirements of such agreements include a high level of resources and tools, which are not feasible across the board for all RDs, so it would be more feasible to restrict them to a limited number of a priori ODs, for example where there are uncertainties and high potential impacts, or when ultra-rare drugs are involved.

### 41. SEEK ALTERNATIVE FUNDING MODELS, NOT LINKED TO SALES/COST

It is proposed that other forms of financing for RD-targeted therapies should be searched and applied, using as an example antibiotics against multidrug-resistant germs. The return on investment would be more closely linked to a series of payment models for reaching certain milestones, and a flat rate for having the therapy available and not for the use/sales of this therapy (subscription model for availability). Hybrid systems could be an option.

**RELEVANCE**

**7.97**

Although these models are still poorly defined, the search for alternative or hybrid systems agreed between payer and company may be a good way to explore this type of complex medicines, as they can help to correct the current situation of RD financing unpredictability and the problem of overpricing due to the need to retrieve the companies' investments and the difficulties of negotiation in a monopoly situation. However, they should only be an alternative available to funders and companies, without radically changing the way these medicines are financed. Others argue that before deciding on their priority, models applied to other processes need to be validated for RDs.

**FEASIBILITY**

**47.5%**

Most experts consider that, being an innovative proposal, it has low feasibility in the short term. It is argued that the population to be treated is very low, so the industry needs to have a clear vision of the return it will get and, for this, the mechanism of return per sale is the clearest. Some experts believe that it would be appropriate to start with a pilot for at least the next 1-2 years, applied to some subgroup of ODs.

### 42. CREATION OF A SPECIFIC STATE FUND FOR RARE DISEASES

This fund, which would be extra-budgetary and estimated a priori, would not be applicable to all RDs, just only to those with certain characteristics and prevalence. The possibility of fitting within the Health Cohesion Fund could also be assessed. A technical committee should identify the medicines to be included, categorising them according to their impact on the NHS.

**RELEVANCE**

**7.06**

Some experts consider that a target fund could be a good measure for certain innovative, but not necessarily rare, medicines. There are concerns about its financial envelope and the definition of the medicines to be included in it. On the other hand, some people point out that silos can be inflationary and that previous experiences in other countries have shown controversial results, so it could not be considered as a 100% effective measure. It would be difficult to justify the creation of a fund for this type of medicine and not for other pathologies, which sometimes have the same price. Although they see it hardly viable in our NHS, if it were to be implemented, very well-defined rules would have to be established so that it would not be a barrier to access to new products.

### 43. COMPLEMENT THE FUNDING DECISION WITH OTHER TOOLS

The funding decision should be complemented with other tools, such as Multi-Criteria Decision Analysis (MCDA), which has already been applied in some AACC for these therapies.

RELEVANCE

7.45

Some experts emphasize that it is necessary to understand that not only how the TPR is involved in the funding decision, but also how the multiple criteria included in the legislation are being taken into account into the final funding decision. Multidimensional valuations are already often incorporated in the discussion of TPRs, so it would be important to identify which criteria can be provided by the MCDA that are not yet taken into account in the decision and to apply methodologies that can standardise the multidimensional valuation.

### 44. EXCLUSION OF ORPHAN DRUGS COST FROM HOSPITAL SPENDING TARGET

It is proposed that medicines for RDs should not be included in the spending targets set by the regional health services for different hospitals.

RELEVANCE

7.28

For some experts, this measure could be favourable, while others consider it counterproductive. On the one hand, it could improve access to these drugs and ensure that there are no barriers to treatment due to local budgetary constraints. On the other hand, others believe that it would promote a more inefficient system, as it could relax vigilance in the management of high-impact medicines, and should not be a stand-alone measure, but should be complemented by other management measures. Moreover, some experts warn that other groups could request the same. Not all experts are in favour of a radical differentiation of RDs from other pathologies.

## AREA 9: MONITORING AND EVALUATION MECHANISMS

### 45. GOVERNANCE OF MONITORING MECHANISMS

Progress should be made on the governance model for monitoring mechanisms, analysing which real-life data should be collected and for what purpose, taking into account its opportunity cost in terms of staff and time. The roles, policies and metrics to be employed should also be specified for a more efficient use.

RELEVANCE

8.38

It is a necessary measure because the decision-making processes in Spain (both at national and regional level) need governance models. For the real-life data collection it is important to introduce a culture of data collection and analysis and to achieve the greatest possible standardisation between hospitals and AACC to guarantee the usefulness of the information, especially in RDs. This requires, among other things, providing expert centres with the necessary resources (staff/time).

FEASIBILITY

67.5%

This is a moderately feasible measure that would require the involvement of clinicians, expert researchers and patient organisations in the design and implementation of the model. Governance models for monitoring mechanisms can and should be defined within the framework of the National Strategy for RDs with the endorsement of the Interterritorial Council. Moreover, new technologies would open up a real option to enable such initiatives.

### 46. SINGLE REGISTRY AT NATIONAL LEVEL

Progress should be made towards an effective single national registry, based on the registry developed by the Instituto de Salud Carlos III (ISCIII) and fed by the different regional registries, with well-defined and unified health data and criteria, and with funding from the state. VALTERMED could also be used as a platform.

RELEVANCE

8.41

Having an effective unique registration is preferable to the current situation of centralised registers in one Autonomous Region or even in one hospital centre, which would avoid duplication of registers and data entry. Centralising information would be a fundamental step in collecting and analysing health outcomes and would also improve overall knowledge. The AACC should have the capacity to use the systems that best adapt to their reality, always guaranteeing interoperability. This could be based on work that has been very well developed by the ISCIII and which would also count on the collaboration of the European Platform of RD Registries. However, in the opinion of one expert, the idea of a single registry is overrated, and he considers that at present it would be sufficient to have access to clinical records.

FEASIBILITY

55.0%

Some experts think that the feasibility of this measure in the short term is limited by the harmonisation between health services, but in the medium term, it would be feasible and would largely depend on the sustained willingness of the administrations. However, it should be borne in mind that there are numerous obstacles, as the collection of real-life data at national level requires coordination and sustained willingness in data collection by professionals involved in patient care. For some, having a national registry of RDs is very feasible, but having such a register as a "unique registration" seems impractical. Others question the reliability of such a single register, while one expert mentions that it would be feasible if the criterion of mandatory registration were incorporated.

### 47. DEFINITION OF THE GROUPS OF THERAPIES TO BE INCLUDED IN THE REGISTRIES

Differential monitoring of financed and non-financed therapies should be carried out, given their different casuistry.

RELEVANCE

6.97

Some experts point out that the situation of funded and unfunded therapies is a changing situation, which will be difficult to manage if differentiated monitoring mechanisms are used.

### 48. SPECIFIC DATA COLLECTION FOR ORPHAN MEDICINAL PRODUCTS

Clinical data should be collected from actual clinical practice, as well as information reported directly by patients. Information on direct and indirect costs, as well as quality of life measures of patients and their carers, should also be stored. Data should also be collected to facilitate research and re-evaluation of therapies. The data should be suitable for use with Big Data (structured information), with the direct involvement of institutions capable of statistical data analysis or experts in knowledge engineering.

**RELEVANCE**

**8.53**

The specific collection of data for RD medicines is a key element to assess their effectiveness, the clinical relevance of the observed benefits and to manage these therapies appropriately. Big data can be an important advance. For some, collected information must be relevant to the established aims and objectives. For others, collection should go beyond structured information, seeking to incorporate unstructured data from medical records. Clinical data should be structured in an interoperable format (between national and, ideally, international centres), quantified, monetised and returned to the NHS. All aspects of data protection must be taken care of. The measure would be general, but would also apply to non-ODs.

**FEASIBILITY**

**52.5%**

This is an extremely important and useful objective that should be led by administrations, but it is not highly feasible in the short term, given its complexity. Feasibility would be low if it includes all medicines (orphan or not) for a RD; whereas feasibility would be higher if it is restricted to a limited number of medicines. For others, it could be feasible if there is transparent collaboration of all stakeholders or if the National Register is used for the collection of patient information, taking into account that staff is needed to collect and manage the data (other than clinicians).

### 49. CREATION OF THE ROLE OF DATA MANAGER

The figure of the data manager should be standardised within each centre of the healthcare system, in order to improve the processing and management of information and spare doctors this bureaucratic task. These managers should be coordinated in the different centres and AACC.

**RELEVANCE**

**8.09**

Some experts consider that it is a controversial measure, due to access to confidential information and the possible errors that could be made by non-health professionals, in addition to the fact that each system can establish the mechanism it considers more appropriate for managing the information, as long as its reliability and traceability are guaranteed. However, this administrative task places an overload on healthcare staff or, in some cases, makes it impossible to keep records or monitoring sheets up to date. For this reason, some experts believe that a data manager may be important to improve the effectiveness and efficiency of information management, especially in the case of RDs. Some point out that the standard characteristics of the data manager should be established at European level. Others do not see this as a priority and believe that automated clinical information capture and cleansing systems should be considered as an alternative.

FEASIBILITY

65.0%

65% of the experts consider it feasible to create this figure, which would help in data validity and reliability. Some believe that this is linked to procedures and the location of the data repository, and that it is not something that can be negotiated by all, but something that is managed by the responsible for the repository in accordance with data protection regulations. However, it would be possible to reach a consensus on procedures. On the other hand, some believe that there are budgetary and cultural barriers, and that it will therefore take a long time for data managers to standardise.

### 50. DIGITALIZATION OF NETWORKS AND ACCESS TO INTERNATIONAL REGISTRIES

Necessary connections must be established to be able to share national and international information. Based on the European Pharmaceutical Strategy, interoperability between national and European databases is essential. The national register should be part of the European platform of RD registers, and should go beyond the regional or national level to a European level.

RELEVANCE

8.59

It is essential to increase knowledge in RDs creating databases and registers with a European scope because for RDs is necessary to guarantee interoperability.

FEASIBILITY

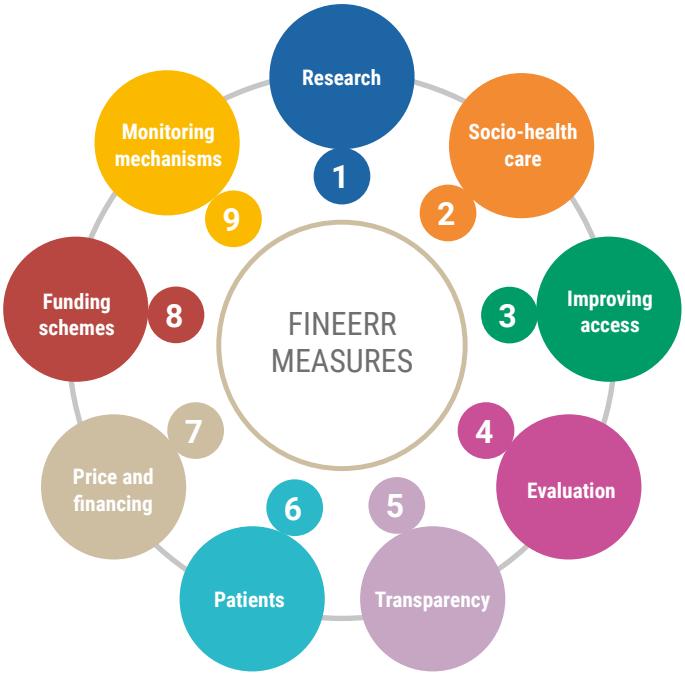
62.5%

The connections are feasible, but their correct implementation would require a better structure, provision and regulation. Currently, the interoperability of the different regional information systems makes it difficult to carry out this measure, but sharing information is key to the progress of research, and regulation should be a precondition for this. For some experts, it needs to be discussed because the recent EU data protection regulation is insufficient, and the regulation of the use of knowledge transfer from the public to the private sector remains unanswered, without the issue of privacy being completely resolved. In this case, it would be a new system of public-private collaboration that needs to be regulated to avoid decapitalising the public sector.

**FIGURE 32. LIST OF THE 50 PROPOSED ACTION MEASURES**

**Note:** This summary simply lists the recommendations proposed by at least one of the experts in the project's WGs, but does not imply that the other experts necessarily agreed with them.

The number of measures only refer to the code number followed by questionnaire.




### 1

1. Reformulate European R&D incentives
2. Enhance RD research
3. Tax incentives for R&D in RDs
4. Improve the administrative and legal conditions for clinical trials
5. Rapid recruitment of patients for clinical trials
6. Public-private collaboration in research
7. Sharing access to neglected industry research

### 2

8. Diagnostic harmonisation between AACC
9. Improve referral processes within and outside CSUR
10. Improving concessions/funding of CSUR
11. Increased incorporation of CSUR into European networks
12. Improve the training of healthcare professionals in RDs
13. Standardised rules of socio-health care

### 3

14. More EMA-FDA collaboration in ODs
15. Establish EU centralised purchasing agreements for ODs
16. National political agreement
17. Effective enforcement of territorial equality
18. Creation of a centralised entity in RDs
19. Specific procedure to access RD-targeted therapies
20. Change administrative silence from negative to positive
21. Matrix to ensure compliance with time limits
22. Penalize lack of diligence in access by the AACC
23. Better access in special situations

### 4

24. Evidence required by EMA for authorisation
25. Minimising impact of cost-effectiveness in funding
26. Powerful statistical analysis of evaluations
27. Dynamic clinical and economic reassessment

### 5

28. Methodology and deadlines for evaluation and access
29. Mandatory TPR publication
30. Transparency in the quantification of funding criteria
31. More transparency in pricing

### 6

32. Greater patient representation/participation in decisions
33. Digital national platform for consultation
34. Validation of specific PROM/PREM scales
35. Better professional-patient communication

### 7

36. Highlighting the social and health value of medicines
37. Uncertainty as a negative value for pricing
38. NHS expertise in price negotiation
39. Tariff models by type of RD

### 8

40. Systematic application of funding mechanisms
41. Alternative funding models
42. . Specific fund at national level for RDs
43. Complement decision with other tools
44. Exclusion of ODs cost from hospital spending target

### 9

45. Governance monitoring mechanisms
46. National registry of RDs
47. Define groups of therapies to be included in registries
48. Specific data collection for ODs
49. Creation of data manager
50. Digitalization of networks and access to international databases

## ANALYSIS OF ACTION MEASURES

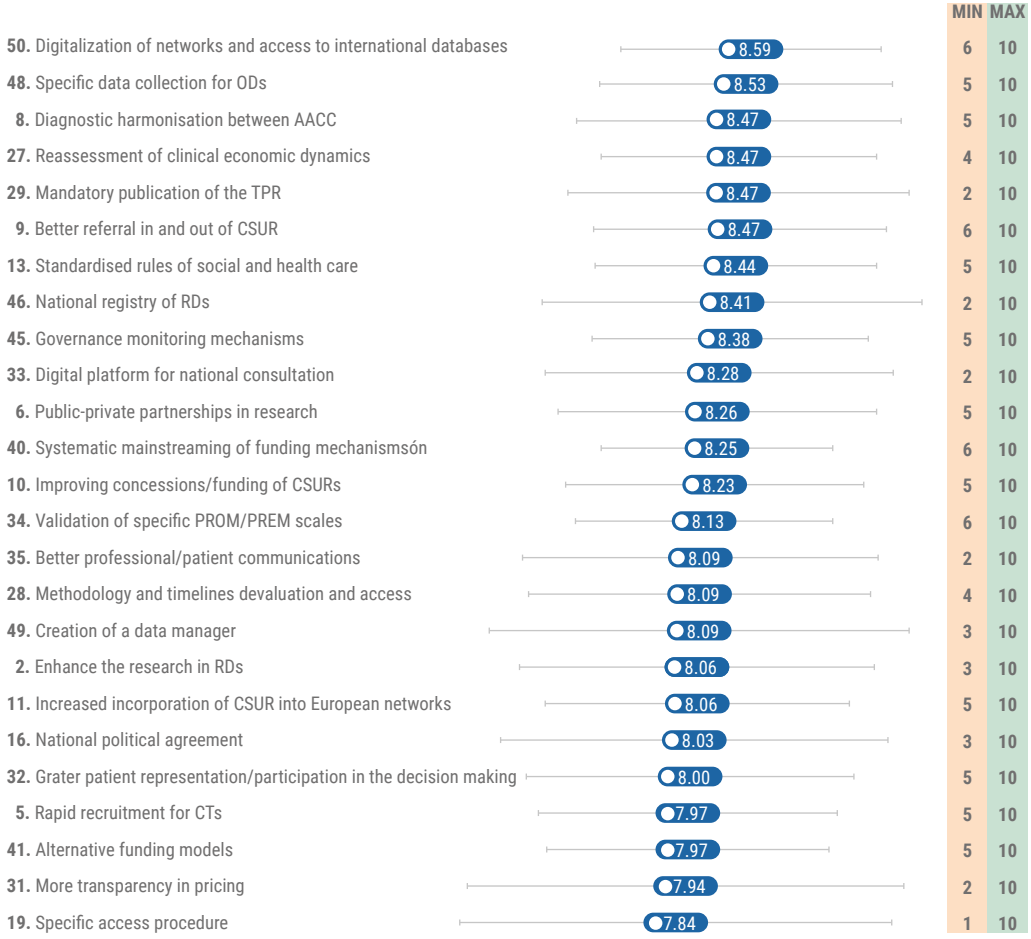
In order to reach a conclusion, once the 50 main action measures proposed by the experts had been grouped together, they were divided into two different groups according to their degree of relevance. First, the CORE and WG1-3 experts (n=32) were asked about the relevance of each of the measures, on the basis of which we grouped the 25 most relevant (recommendations) and the 25 least relevant measures. In a second round, the experts were asked to assess the feasibility of implementing the 25 most relevant actions arised in the previous step.

The measure considered most relevant overall (with an average score of 8.59 out of 10) is related to the digitalization of networks and access to international databases. This is followed by the specific collection of data for ODs (8.53) and diagnostic harmonisation between AACC (8.47) (Figure 33). It should be noted that 4 of the 10 most relevant measures form part of the "monitoring mechanisms" area (digitalization of networks, specific data collection for ODs, single national registry and governance of monitoring mechanisms); and that another 3 measures in the top 10 correspond to the area of "socio-health care" (diagnostic harmonisation, better referral between centres and standardised socio-health care norms at the national level). These are the two areas with the highest average scores for relevance (Figure 35).

**FIGURA 33. THE 25 ACTION MEASURES CONSIDERED MOST RELEVANT (RECOMMENDATIONS)**

**Note:** these responses are based on the opinion of CORE and WG1-3 experts (n=32).

The figure shows the average score and the standard deviation, also the minimum and máximum scores reported for each measure.



Among the 25 recommendations, those with the greatest consensus among experts (lowest standard deviation) were those referring to the systematic incorporation of financing mechanisms (SD: 1.11), validation of specific PROM/PREM scales (SD: 1.24) and network digitalization (SD: 1.27). On the other hand, those with less consensus were those relating to greater transparency in pricing (SD: 2.11), specific access procedure (SD: 2.08) and the creation of the role of data manager (SD: 2.04).

On the other hand, the measures considered less relevant by the experts were those related to changing administrative silence from negative to positive (6.0 out of 10) and penalising the lack of diligence in access by the AACC (6.42) (Figure 34). Four of the 10 least relevant measures refer to the area of "improving access", as they could generate undesirable effects such as, for example, lengthening access times (greater collaboration between EMA and FDA, creation of a centralised entity in RDs, changing administrative silence and penalising a lack of diligence (Figure 35). Regarding the degree of consensus of this block of measures, those with the highest dispersion were changing administrative silence (SD: 3.0), the exclusion of ODs from hospital expenditure (SD: 2.88) and the strongest evidence required by the EMA for drug authorisation (SD: 2.67).

**FIGURE 34. THE 25 ACTION MEASURES CONSIDERED LEAST RELEVANT**

**Note:** these responses are based on the opinion of CORE and WG1-3 experts (n=32).

The figure shows the average score and the standard deviation, also the minimum and máximum scores reported for each measure.

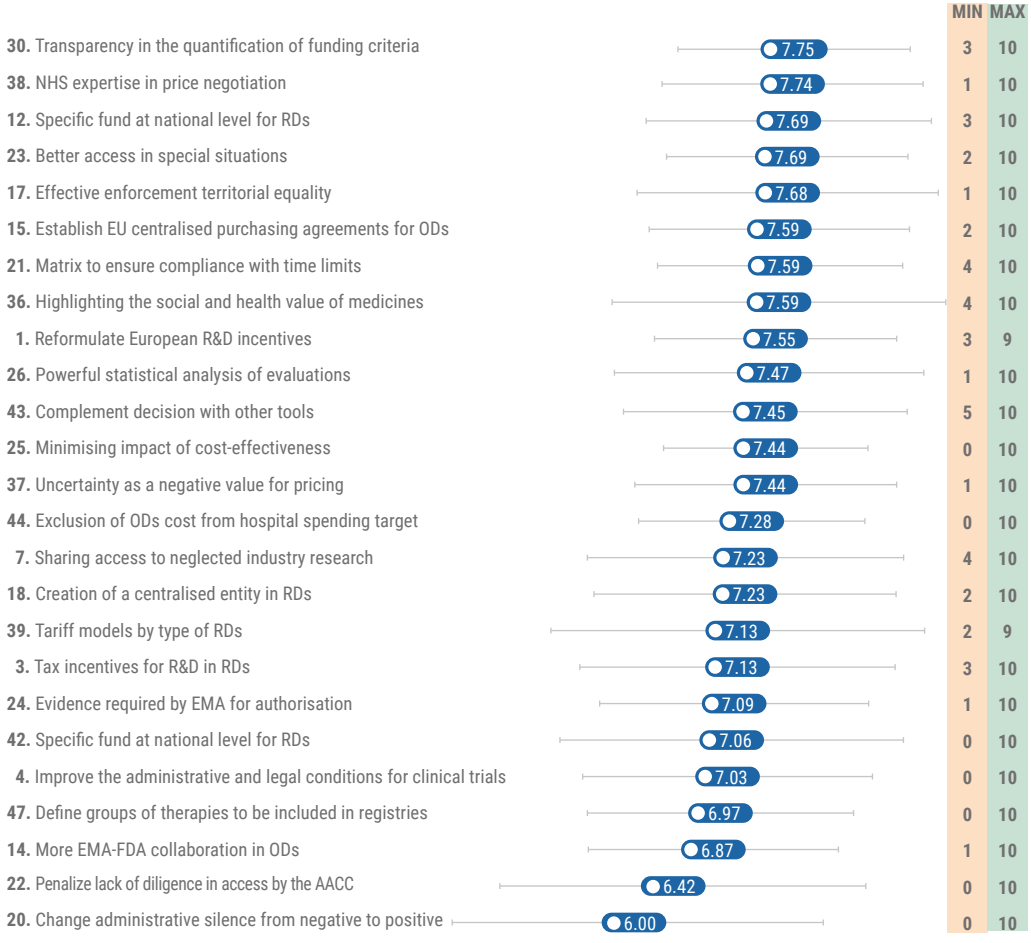
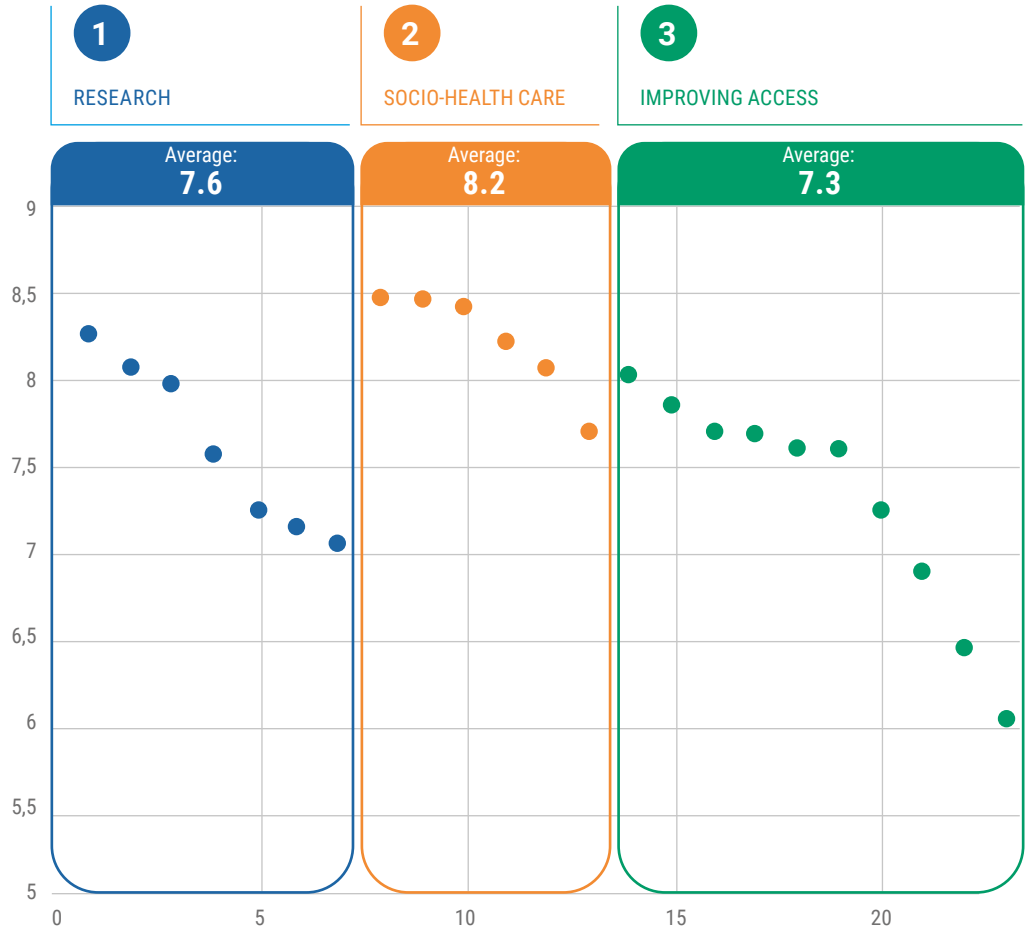


**FIGURE 35. THE 50 PROPOSED ACTION MEASURES, SORTED BY THEMATIC AREA AND RELEVANCE**

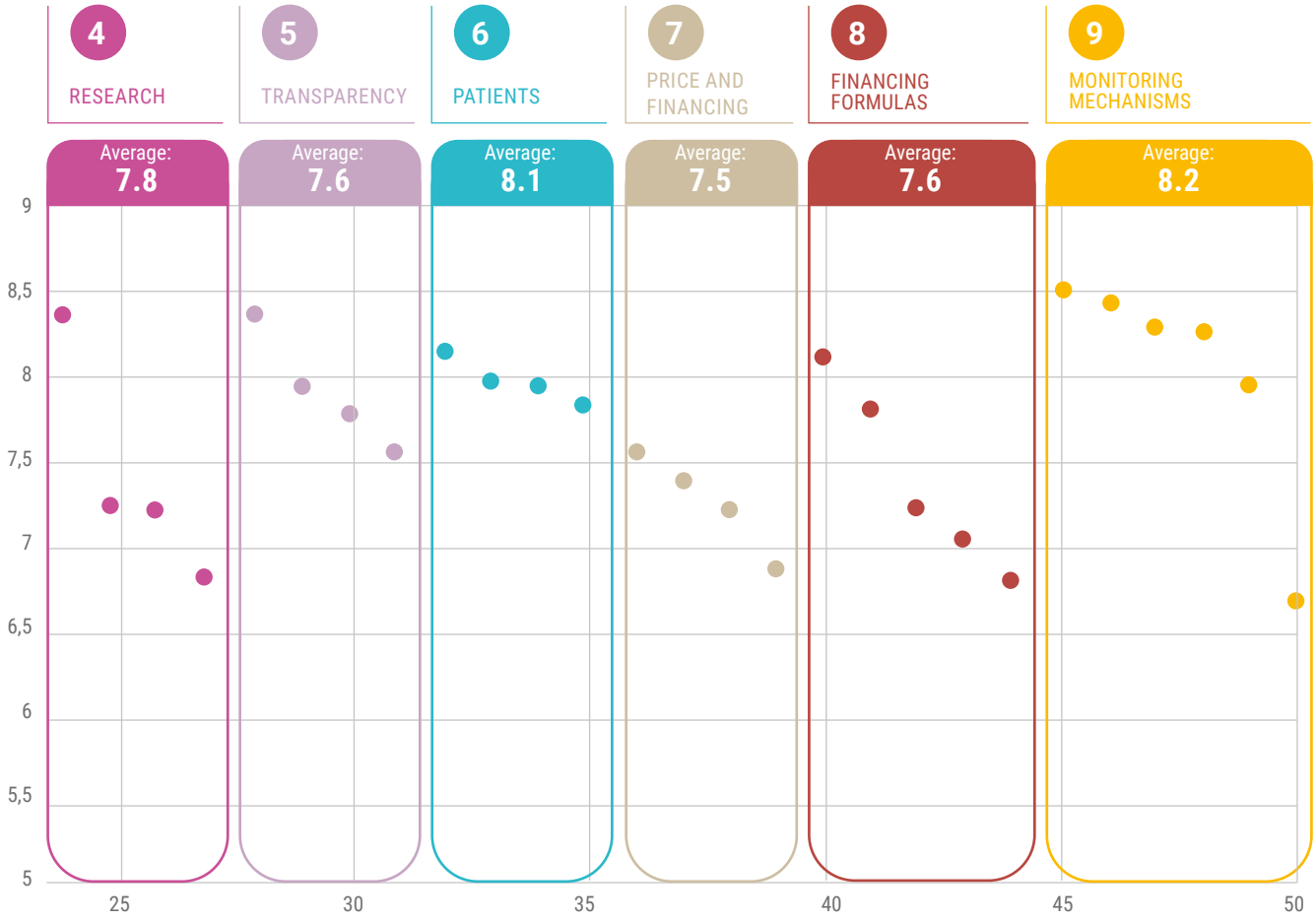
**Note:** This summary simply lists the recommendations proposed by at least one of the experts in the project's WGs, but does not imply that the other experts necessarily agreed with them. These responses are based on the opinion of CORE and WG1-3 experts (n=32).




**6.** Public-private collaboration in research
**2.** Enhance the research in RDs
**5.** Rapid recruitment for CTs
**1.** Reformulate European R&D incentives
**7.** Sharing access to neglected industry research
**3.** Tax incentives for R&D in RD
**4.** Improve the administrative and legal conditions for clinical trials

**8.** Diagnostic harmonisation between AACC
**9.** Improve referral processes within and outside CSUR
**13.** Standard rules of socio-health care
**10.** Improving concessions/funding of CSUR
**11.** Increased incorporation of CSUR into European networks
**12.** Improve the training of healthcare professionals in RDs

**16.** National political agreement to RD-targeted therapies
**19.** Specific access procedure
**23.** Better access in special situations
**17.** Effective enforcement of territorial equality
**15.** Establish EU centralised purchasing agreements for ODs
**21.** Matrix to ensure compliance with time limits
**18.** Creation of a centralised entity in RDs
**14.** More EMA-FDA colaboration
**22.** Penalize lack of diligence in access by the AACC
**20.** Change administrative silence from negative to positive




**27.** Dynamic clinical and economic reassessment
**26.** Powerful statistical analysis of evaluations
**25.** Minimising impact cost-effectiveness
**24.** Evidence required by EMA for authorisation

**29.** Mandatory TPR publication
**28.** Methodology and deadlines for evaluation and access
**31.** More transparency in pricing
**30.** Transparency in the quantification of funding criteria

**33.** Digital platform for national consultation
**34.** Highlighting the social and health value of medicines
**35.** Professional-patient communication
**32.** Grater patient representation/ participation

**38.** NHS expertise in price negotiation
**36.** Highlighting the social and health value of medicines
**37.** Uncertainty as a negative value for pricing
**39.** Tariff models by type of RD

**40.** Systematic application of funding mechanisms
**41.** Alternative funding models
**43.** Complement decision with other tools
**44.** Exclusion of ODs cost from hospital spending target
**42.** Specific fund at national level for RDs

**50.** Digitalization of networks and access to international databases
**48.** Specific data collection for ODs
**46.** National registry of RDs
**45.** Governance of monitoring mechanismso
**49.** Creation of data manager
**47.** Define groups of therapies to be included in registries

### RELEVANCE OF THE MEASURES FOR THE CORE GROUP

Four of the 10 most relevant measures for the CORE Group were also relevant for the thematic WGs experts. These were dynamic reassessment, improved referral, specific data collection for ODs and mandatory publication of the TPR. On the other hand, there was more disagreement on the relative relevance of measures such as the reconsideration of the EMA's drug authorisation requirements or increased transparency in pricing.

| MEASURE | CORE RANKING | WG RANKING |
|---|---|---|
| 13. Standardised rules of socio-health care | 1st | 10th |
| 31. More transparency in pricing | 2nd | 32nd |
| 40. Systematic application of funding mechanisms | 3rd | 18th |
| 27. Dynamic clinical and economic reassessment | 4th | 8th |
| 6. Public-private collaboration in research | 5th | 17th |
| 9. Improve referral processes within and outside CSUR | 6th | 7th |
| 48. Specific data collection for ODs | 7th | 4th |
| 29. Mandatory TPR publication | 8th | 5th |
| 24. Evidence required by EMA for authorisation | 9th | 48th |
| 33. Digital platform for national consultation | 10th | 15th |

**Note:** The numbers of the measures only refer to their numerical code in the questionnaire

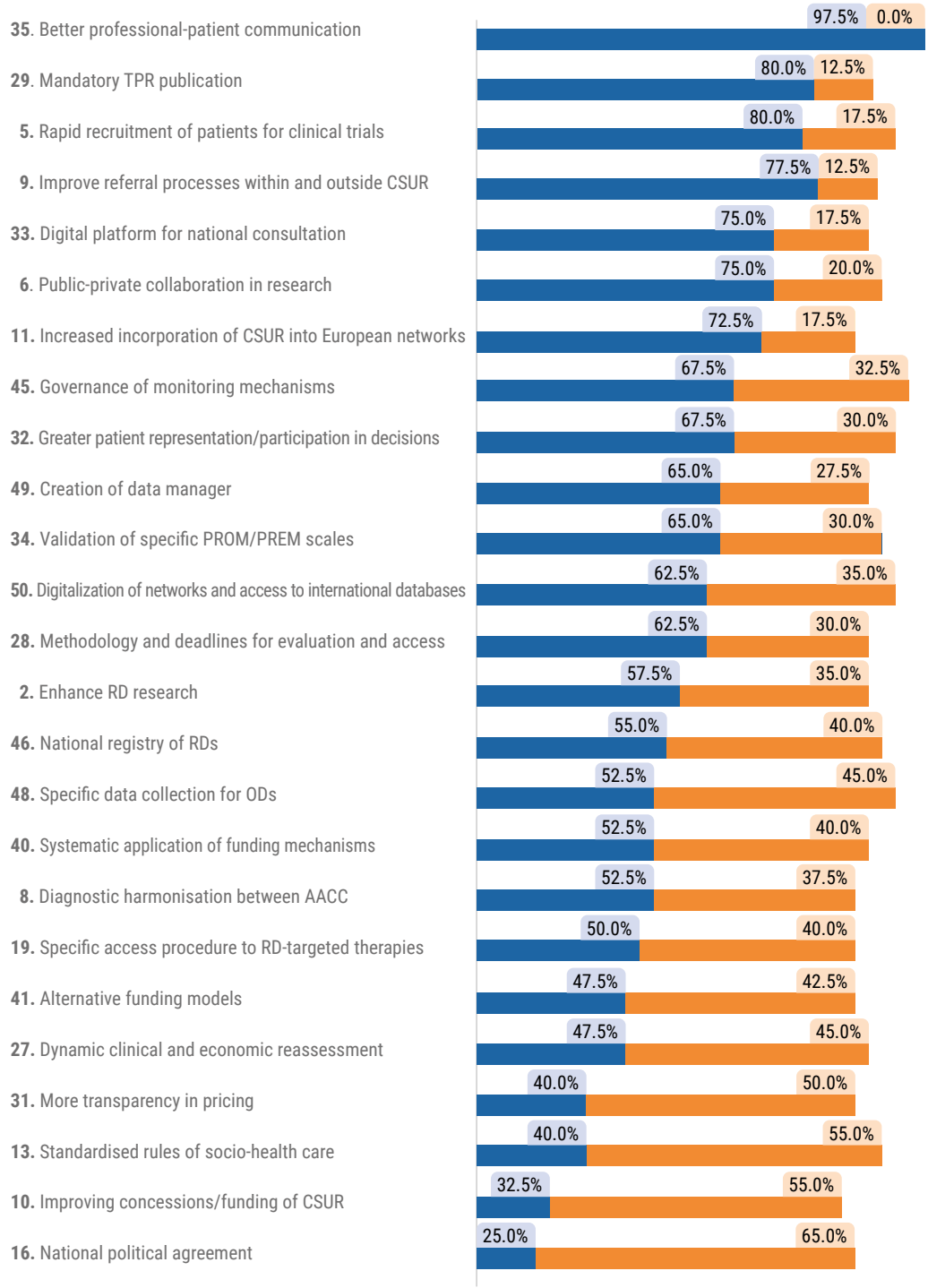
Below, we show the feasibility of implementing the 25 recommendations for action. In general terms, for the FINEERR experts, the most feasible measure would be to promote greater communication between healthcare professionals and patients, since, despite its lack of concreteness, 97.5% considered it to be highly feasible. This will require healthcare staff to be able to devote more time to their patients and to the study of rare pathologies. Other measures of high feasibility are the mandatory publication of the TPR (also among the 10 most relevant) and the rapid recruitment of patients for clinical trials (of intermediate relevance) (Figure 36).

In contrast, only 25% of the experts considered it feasible to implement a political agreement at national level on RDs, given the current political landscape, with an institutional agreement by the central and regional administrations being more feasible. Other measures such as improving the funding and concessions of the CSURs and standardisation of social and health care do not seem very feasible either.

**FIGURE 36. THE 25 MOST RELEVANT ACTION MEASURES (RECOMMENDATIONS), RANKED BY FEASIBILITY**

- % of respondents indicating high feasibility
- % of respondents indicating low feasibility

**Note:** these answers are based on the opinion of the 40 experts of the FINEERR project.



## FEASIBILITY OF MEASURES FOR THE CORE GROUP

Six of the 10 measures considered most feasible by the CORE Group were also considered most feasible by the rest of the WG experts, being therefore more aligned in terms of feasibility than in terms of relevance. The measures with the greatest agreement on their high feasibility are those relating to greater communication between agents, strengthening public-private collaboration, improving referral, rapid recruitment of patients for clinical trials, greater internationalisation of CSURs and mandatory publication of the TPR. The greatest discrepancy in this top-10 of feasibility was the systematic application of funding mechanisms for these therapies.

| MEASURE | CORE RANKING | WG RANKING |
|---|---|---|
| 35. Professional-patient communication | 1st | 1st |
| 6. Public-private collaboration in research | 2nd | 6th |
| 8. Diagnostic harmonisation between AACC | 3rd | 18th |
| 9. Improve referral processes within and outside CSUR | 4th | 5th |
| 40. Systematic application of funding mechanisms | 5th | 20th |
| 50. Digitalization of networks and access to international databases | 6th | 15th |
| 5. Rapid recruitment of patients for clinical trials | 7th | 2th |
| 11. Increased incorporation of CSUR into European networks | 8th | 7th |
| 29. Mandatory TPR publication | 9th | 3th |
| 2. Enhance RD research | 10th | 14th |

**Note:** The numbers of the measures only refer to their numerical code in the questionnaire

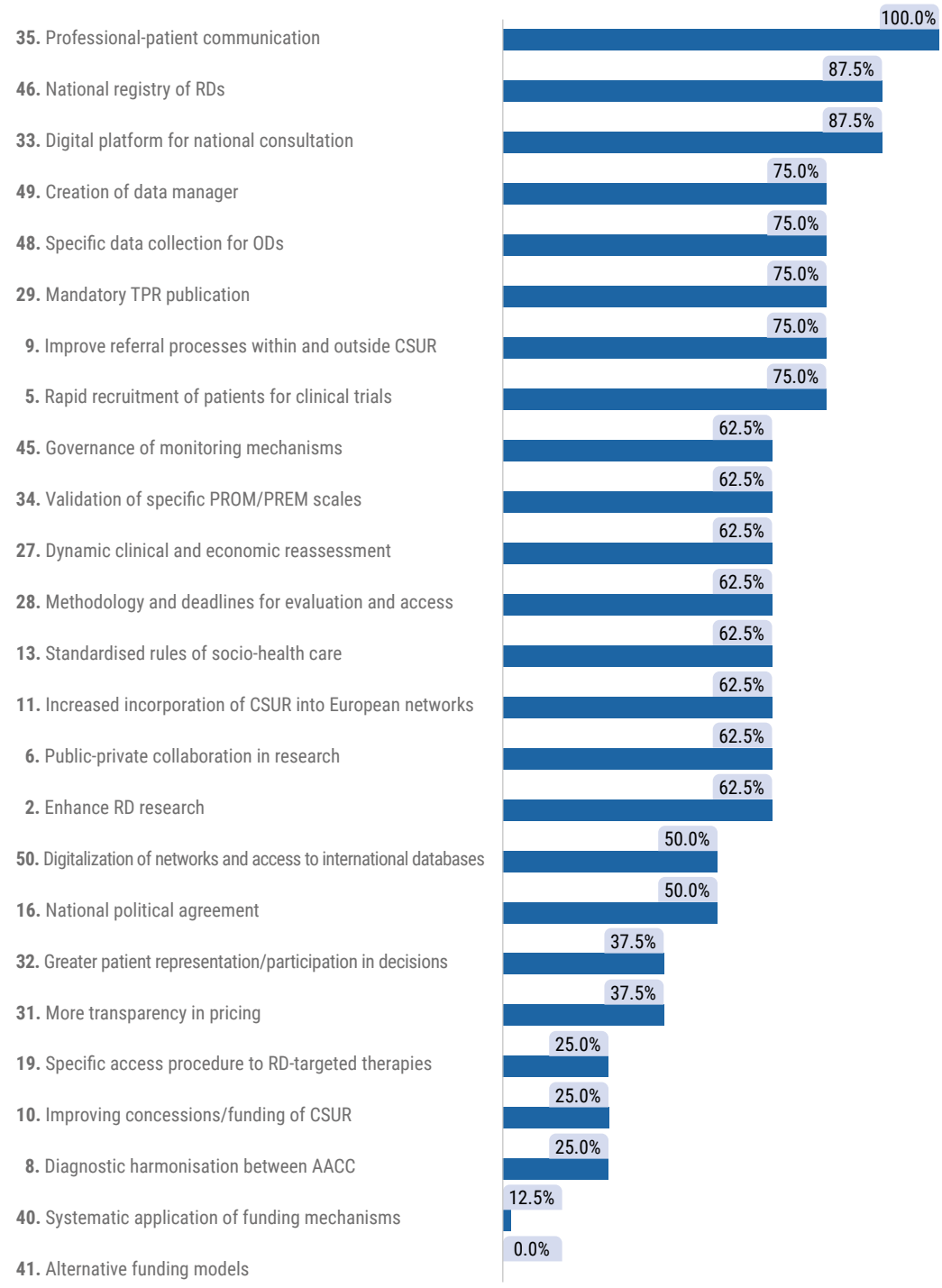
## FEASIBILITY OF MEASURES FOR WORKING GROUP 4

The objective of WG4 was to discuss the implementation of a new funding model to access RD therapies model in Spain, so it may also be of interest to know the particular view of this group of active managers and politicians on the feasibility of the measures considered globally more relevant.

This group of experts agreed with the others regarding that the most easily implementable measure is the improvement of professional-patient communication (Figure 37). The next most feasible measures for WG4 were related to data monitoring (single registry, consultation platform, creation of the role of data manager and specific data collection for RDs). On the other hand, the least feasible would be the implementation of alternative funding models not linked to sales or cost, where they disagree with the other experts. On the other hand, half of the experts in WG4 believe that it is relatively feasible to reach a political agreement at national level, which is a good sign for progress in the area of funding and access to these therapies in Spain.

**FIGURE 37. WG4'S VIEW ON THE FEASIBILITY OF THE 25 MOST RELEVANT MEASURES**

■ % of experts of WG4 who assessed the action measure as "highly feasible"




To facilitate the understanding of the association between the relevance and feasibility of the different measures, Figure 38 shows the 25 recommendations according to their degree of feasibility. In the **upper right quadrant** there are the most relevant and feasible proposals according to the experts, and which therefore, given their high importance and feasibility, should be taken into account. They refer to the mandatory publication of TPR, to ensure transparency; the improvement of referral processes for patients with RD within and outside the CSUR, which would enhance the quality and equity of the system; improving the governance of monitoring

mechanisms, analysing what real-life data should be collected and what they are going to be used for; and improving communication between health professionals and patients to increase the knowledge of both agents (Table 7). All of them belong to different thematic areas.

**TABLE 7. THE FOUR MOST RELEVANT AND FEASIBLE MEASURES**

| MEASURE OF ACTION | RELEVANCE | FEASIBILITY |
|---|---|---|
| 29. Mandatory TPR publication | 8.47 | 80.0% |
| 9. Improve referral processes within and outside CSUR | 8.47 | 77.5% |
| 45. Governance of monitoring mechanisms | 8.38 | 67.5% |
| 35. Better professional-patient communication | 8.09 | 97.5% |

**Note:** The numbers of the measures only refer to their numerical code in the questionnaire

On the other hand, the **lower left quadrant** shows the recommendations of less relevance and feasibility (e.g. national political agreement, specific access procedure for RD or more transparency in pricing). Regarding the national political agreement, the low feasibility is explained by the fact that experts believe that it is difficult to reach a major political agreement at national level. As for the specific access procedure, its low feasibility is due to the complexity of the current financing and access system and the fact that, according to the experts, our healthcare administrations are not yet ready to achieve such an innovative objective.

The **lower right quadrant** represents the most feasible but the least relevant measures, such as greater professional-patient communication, rapid patient recruitment mechanisms, public-private collaboration in research or greater incorporation of CSURs in European networks.

Finally, in the **upper left quadrant** shows the most relevant actions, although their feasibility of implementation is only intermediate, for different reasons. This is the case of measures such as better financing of CSUR, diagnostic harmonisation, standardisation of social and health care norms or dynamic clinical and economic reassessment. Regarding the former, experts believe that its real feasibility is undermined by the territorial organisation of the State, while regarding dynamic reassessment, some experts believe that it is difficult to design and coordinate models.

If we analyse these same results according to the area to which the measures belong to (Figure 39), the areas of social and health care and follow-up mechanisms are those with the highest number of relevant measures. According to the feasibility, the recommendations in the area of patients have the highest average of feasibility, with all measures in the right quadrant, although their average relevance is moderate. Other areas with highly feasible measures are research and transparency. In contrast, the least feasible measures are found in the areas of improving access and funding schemes.

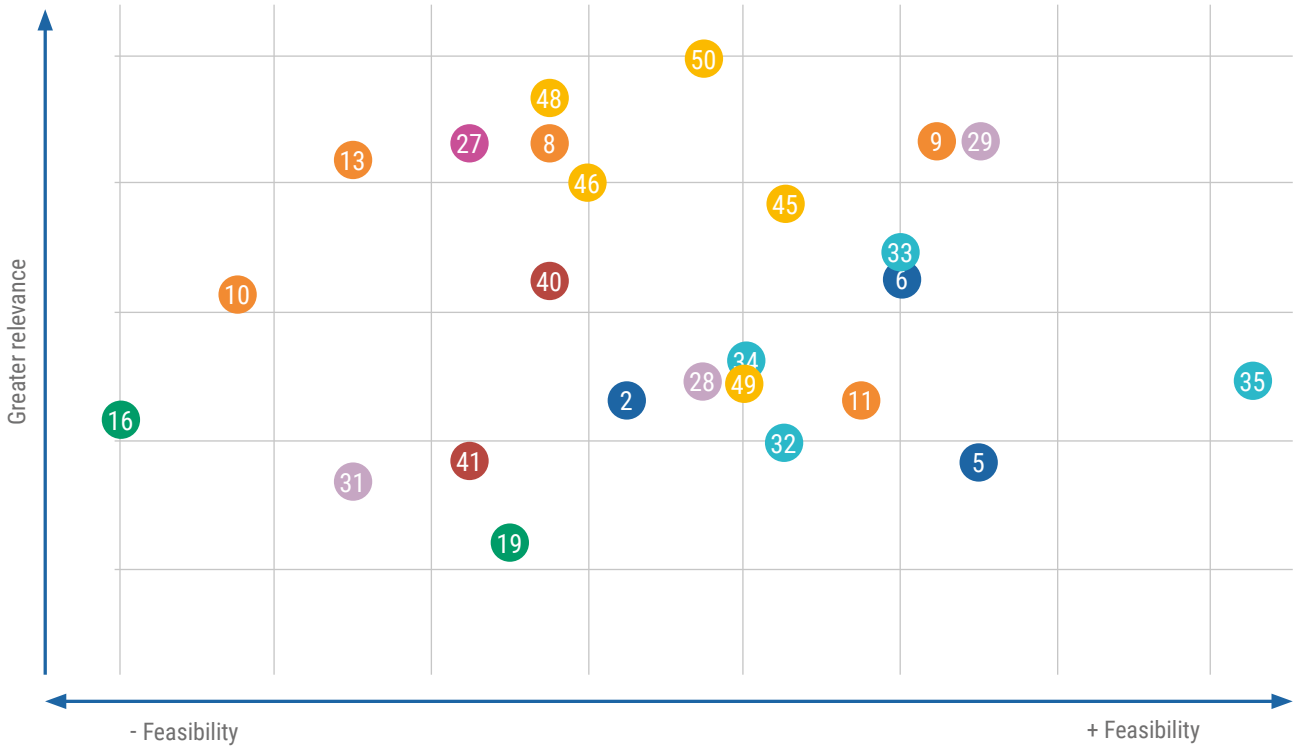



**FIGURE 38. THE 25 RECOMMENDATIONS (MOST RELEVANT MEASURES), PLOTTED BY DEGREE OF FEASIBILITY**

- **AREA 1:** Research
- **AREA 2:** Socio-health care
- **AREA 3:** Improving access
- **AREA 4:** Evaluation
- **AREA 5:** Transparency
- **AREA 6:** Patients
- **AREA 8:** Financing formulas
- **AREA 9:** Monitoring mechanisms

**2.** Enhance RD research
**5.** Rapid recruitment of patients for CTs
**6.** Public-private collaboration in research

**8.** Diagnostic harmonisation between AACC
**9.** Improve referral processes within and outside CSUR
**10.** Improving concessions/funding of CSUR
**11.** Increased incorporation of CSUR into European networks
**13.** Standardised rules of socio-health care

**16.** National political agreement
**19.** Specific access procedure to RD-targeted therapies

**27.** Dynamic clinical and economic reassessment

**28.** Methodology and deadlines for evaluation and access

**29.** Mandatory TPR publication
**31.** More transparency in pricing

**32.** Greater patient representation/participation
**33.** Digital platform for national consultation
**34.** Validation of specific PROM/PREM scales
**35.** Better professional-patient communication

**40.** Systematic application of funding mechanisms
**41.** Alternative funding models

**45.** Governance of monitoring mechanisms
**46.** National registry of RDs
**48.** Specific data collection for ODs
**49.** Creation of data manager
**50.** Digitalization of networks and access to international databases




**FIGURE 39. THE 25 RECOMMENDATIONS (MOST RELEVANT MEASURES), PLOTTED BY DEGREE OF FEASIBILITY, ACCORDING TO THE AREA TO WHICH THEY BELONG**

**2.** Enhance RD research
**5.** Rapid recruitment of patients for CTs
**6.** Public-private collaboration in research

**8.** Diagnostic harmonisation between AACC
**9.** Improve referral processes within and outside CSUR
**10.** Improving concessions/funding of CSURs
**11.** Increased incorporation of CSUR into European networks
**13.** Standardised rules of socio-health care

**16.** National political agreement
**19.** Specific access procedure to RD-targeted therapies

**27.** Dynamic clinical and economic reassessment

**28.** Methodology and deadlines for evaluation and access

**29.** Mandatory TPR publication
**31.** More transparency in pricing

**32.** Greater patient representation/participation
**33.** Digital platform for national consultation
**34.** Validation of specific PROM/PREM scales
**35.** Better professional-patient communication

**40.** Systematic application of funding mechanisms
**41.** Alternative funding models

**45.** Governance monitoring mechanisms
**46.** National registry of RDs
**48.** Specific data collection for ODs
**49.** Creation of data manager
**50.** Digitalization of networks and access to international databases

# 6

# CONCLUSIONS

We are at an opportune moment for change. It is been 20 years since the specific regulation to promote ODs was put in place in Europe, and we are in a period of transition towards a reformulation of incentives, both at EU and national level. In addition to this, there are other trends of change towards greater precision and cost of treatment and digitalization of the system. All of this within the biggest economic, social and health crisis of the last century, promoted by the COVID-19 pandemic. We must identify bottlenecks and learn from good practices at national and international level, to try to optimise the system in terms of efficiency, equity and sustainability.

FINEERR is a think-tank designed to address a strategic and joint reflection by 40 experts on the challenge of funding and access to RD therapies in Spain from the perspective of the public administrations and health services. The multidisciplinary nature of the WGs help to approach the subject from a multisectoral perspective, with a holistic vision at micro, meso and macro levels. This forum for reflection and debate has made it possible to analyse the problems, discuss the different challenges and levers for change, and propose a number of specific recommendations for action to improve the funding and access to RD therapies in the NHS.

In any case, this is a very complex issue, with multiple factors and involved actors at different levels. Therefore, some of the measures proposed are more general, while others are more concrete. Most of them require political will to put them into practice, and it is neccesary to solve reluctance and other barriers for its implementation. Moreover, in many cases, changes in the functioning of the system at a general level could also benefit RD therapies, while in other cases it seems that improvement should be directed towards specific actions.

From the reflections and recommendations that emerged throughout the project, we can conclude the following ten final considerations:

# CONCLUSIONS

1. **Differentiation between the different RDs.** Not all RDs are the same, and in order to address them, a clear distinction should be made between them, paying special attention to the ultra-rare ones, and giving greater incentives to those with greater unmet needs and potentially more innovative in the field of ODs.

2. **More empowered and participatory patients.** The involvement of patients in decision-making processes is essential to ensure their integration as relevant stakeholders and to enrich perspectives, provide credibility and enhance the transparency of decisions. At the same time, the system must improve the information that the patient receives as an "expert". Although this would need to be specified, greater two-way communication between patients and healthcare professionals would be beneficial for all. On the one hand, for the patient to better understand his or her pathology and treatment, and to feel more involved. On the other hand, for the professional to better understand the casuistry of each case and make the best choice of treatment. To this end, it is necessary to deepen the training of all agents. Progress must also be made in measuring patient-reported outcomes and experiences as a complementary way of measuring health outcomes.

3. **Comprehensive health care.** The CSUR are a fundamental part of the care management of many RD patients and an appropriate distribution and definition of their needs would be desirable. In addition to improving their funding, progress should be made towards greater incorporation of these centres into European networks, in order to take advantage of the knowledge generated and encourage better treatment. In any case, patient care should be comprehensive, including the social, family, educational, medical and pharmacological spheres, for which socio-health care standards should be standardised.

4. **More powerful, collaborative and attractive R&D.** RD research should be promoted at national and international level, allocating more financial resources, with possible tax incentives from the early stages. Administrative and legal barriers to clinical trials should also be reduced, favouring patient recruitment. All of this should be done by promoting a collaborative framework in which the academic, industrial and hospital sectors work in coordination, improving predictability and optimising resources.

5. **More agile and transparent decision-making processes.** From the point of view of public administrations, it is important to speed up the time required for the financing and access to medicines, especially when patients do not have therapeutic alternatives, for example through a specific access procedure. Improving transparency is essential, in the pricing process (with greater standardisation of the criteria and weight ranges to be considered) and in the methodology and timelines of the TPRs and in the subsequent regional and hospital pharmacotherapeutic committees, in order to achieve better effective access to ODs.

**6** **Increase harmonisation of processes for territorial equity.** The legal precept of equitable access should be made effective through more homogeneous and coordinated management and reduction of variability in actual clinical practice. This includes the harmonisation of diagnostic processes, referral and social-health care and access to treatments, in search of greater excellence and equity in the care of patients with RD, with an emphasis on the extension of molecular diagnostics and personalised precision medicine.

**7** **Value-based financing and economic evaluation.** Efficiency is a relevant criterion to be taken into account for funding but in particular in serious diseases with no alternatives, other criteria, such as ethical and humanistic ones, must also have an important weight in the decision. On the other hand, in RD-targeted therapies, evaluations should be carried out from the perspective of society, considering other costs beyond the direct costs of the intervention. A robust uncertainty analysis will be key to quantify the lack of information and to adequately manage the clinical and economic uncertainty inherent to these therapies.

**8** **Funding conditional on uncertainty.** The funding of all therapies associated with uncertainty (therefore, a large part of the RDs) should ideally be linked to a financing mechanism that shares the risks between the Administration and the commercialising laboratory. Progress could also be made on alternative forms of financing, where the return on investment is more closely linked to certain milestones and not so much to sales, in order to obtain more balanced prices. The desirability and feasibility of a possible national extra-budgetary fund applicable to certain innovations, including RD, with certain predetermined characteristics, is being discussed without clear agreement.

**9** **Digitalization and dynamic reassessment.** It is particularly relevant to carry out a specific collection of clinical data from actual practice for RD medicines, allowing a dynamic re-evaluation of clinical and economic outcomes. Progress should be made towards a single registry or national digital platform with well-defined and unified criteria and structured information that allows the use of Big Data, based on appropriate prior governance. To this end, the processing and management of information must be improved and health professionals must be released from this administrative task. Furthermore, the necessary connections must be established to make progress in the interoperability of data at national and international level. On the other hand, it is important to incorporate information directly reported by patients, as well as a greater methodological development for it.

**10** **More than good intentions.** In order to implement changes, leadership and coordination at all levels are necessary. The political will is the beginning of the road. A national agreement would be ideal as a framework to fit together and coordinate actions, with a National RD Strategy resourced and implemented in a timely and equitable manner. The main political groups have shown their agreement on improving the situation of people with RDs, although they disagree on how to approach it. Good governance would define from the beginning the roles, policies and metrics to achieve an efficient use of resources, without losing sight of assessing the progress made.

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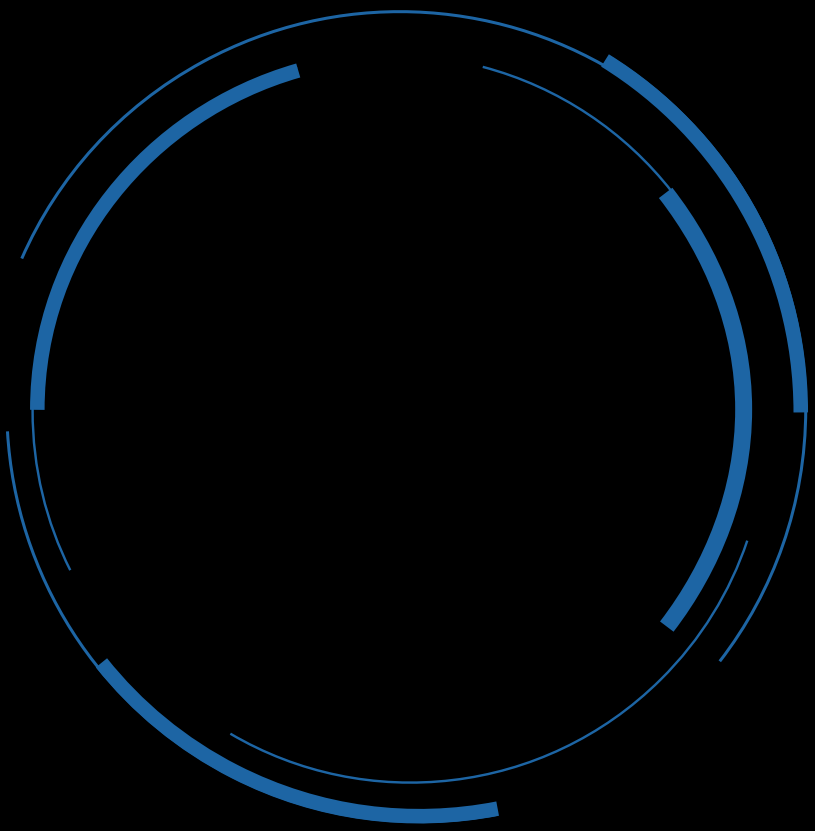
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