Copenhagen Economics

AN EU ACCESS TOOLBOX FOR ORPHAN MEDICINAL PRODUCTS THAT ENABLES EARLY AND EQUITABLE ACCESS

European Expert Group on Orphan Drug Incentives

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European Expert Group on OD Incentives

About the Expert Group

Established in 2020, the European Expert Group on Orphan Drug Incentives (OD Expert Group) brings together representatives of the broad rare disease community, including researchers, academia, patient representatives, members of the investor community, rare disease companies and trade associations.

The initiative is led by a steering group composed of the European Organisation for Rare Diseases (EURORDIS), the voice of people living with a rare disease in Europe, and the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE), representing several companies focused on finding new therapies for rare diseases. The group is chaired by Professor Maurizio Scarpa, Coordinator of the European Reference Network for Hereditary Metabolic Disorders (MetabERN).

Copenhagen Economics serves as a knowledge partner to this initiative.

Since 2020, the Group has published the following reports:

- Orphan medicine incentives. How to address the unmet needs of rare disease patients by transforming the European OMP landscape, 2021, see link
- An operational framework for the modulation of orphan medicine incentives, 2022, see link
- EU HTA fit for rare diseases. Clinical evidence in Joint Clinical Assessments, 2024, see link
- EU HTA fit for rare diseases. Stakeholder involvement in Joint Clinical Assessments, 2024, see link

About this Report

In this report, the OD Expert Group identifies best practices in the access toolbox for OMPs and provides a set of policy actions at the EU level that need to be taken to foster the adoption of such practices among Member States.

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Disclaimers

This report may not reflect in detail the views of every individual member of the OD Expert Group.

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List of main acronyms

AAP	Early Access Authorisation/Autorisation d'Accès Précoce (France)
ATMP	Advanced therapy medicinal product
CUP	Compassionate use programme
EAP	Early access programme
EC	European Commission
EMA	European Medicines Agency
EHDS	European Health Data Space
ERN	European Reference Network
EU	European Union
EUCOPE	The European Confederation of Pharmaceutical Entrepreneurs
EUnetHTA	European Network for Health Technology Assessment
HAS	Haute Autorité de Santé/The French National Authority for Health
HTA	Health Technology Assessment
IQWiG/G-BA	Institute for Quality and Efficiency in HealthCare/Gemeinsamer Bundesausschuss (Germany)
JCA	Joint Clinical Assessments
JSC	Joint Scientific Consultations
MA	Marketing Authorisation
MoCA	Mechanism of Coordinated Access
NIHR	National Institute of Health Research Innovation Observatory (UK)
NICE	National Institute for Health and Care Excellence (UK)
ODD	Orphan Drug Designation
OMP	Orphan Medicinal Products
P&R	Pricing and reimbursement
RCT	Randomised controlled trial
RWD	Real-world data
RWE	Real-world evidence

Glossary of key terminology in this report

Compassionate use	The use of an unauthorised medicine outside a clinical study for an individual patient under strictly controlled conditions. This helps to make medicines that are still under development available to patients.
EU Marketing Authorisation	The approval to sell a medicine in the European Union (EU) or the European Economic Area (EEA). It ensures that the medicine is safe, effective, and of high quality.
Orphan Drug Designation	A status assigned to a medicine intended for use against a rare condition. The medicine must fulfil certain criteria for designation as an orphan medicine so that it can benefit from specific incentives.
Real-world data	Observational data stored in repositories such as electronic health records and disease registries.
Real-world evidence	Evidence on the usage and potential benefits or risks of a medical product derived from analysis of real-world data.

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Access to Orphan Medicinal Products varies greatly across EU Member States

Since 2000, the European Union (EU) has authorised nearly 260 orphan medicinal products (OMPs), offering significant benefits for people living with rare conditions that are life-threatening or chronically debilitating in terms of clinical impact or care.[1] However, access to these OMPs still varies greatly across EU Member States, and many people living with a rare disease in the EU either do not have, or face significant delays in access to, the treatments they need.[2]

Current access policies fail to address the multifaceted barriers that prevent or delay access

To improve this situation, policymakers proposed supply-side measures to incentivise pharmaceutical companies in the revision of the EU General Pharmaceutical Legislation to accelerate product launch and distribution across the EU. These include the European Commission's proposal for a "launch conditionality", whereby granting the IP incentives is conditional upon launching and continuously supplying a medicine in all EU Member States within two years (or three years for SMEs) of marketing approval. A proposal from the European Parliament obliges pharmaceutical companies to file for pricing and reimbursement (P&R) decisions in all requesting EU Member States within a defined timeframe after receiving centralised marketing approval. [3, 4]

This approach neglects the fact that the barriers preventing and delaying patient access to medicines are multifaceted. They stem not only from the supply side, but also from the demand side, involving policies, processes, and decisions that fall under the exclusive competence of the respective EU Member States.[5]

The distribution of competencies in healthcare policy between the EU and its Member States means that solutions capable of improving access cannot only come from EU policymakers. They require parallel action at the Member State level. For example, the current P&R process often takes a long time before a decision on P&R is taken. This is primarily due to the uncertainty around clinical effectiveness inherent to rare and complex diseases with small patient populations. Yet, the limited clinical evidence does not allow fully informed P&R decisions.

Effective policy solutions must therefore consider both supply-side and demand-side factors and be implemented at the Member State level.

The OD Expert Group has developed an access toolbox based on Member States' best practices

Against this background, the European Expert Group on Orphan Drug Incentives (OD Expert Group) has come together to

- identify best practices for generating faster and more equitable patient access to medicines that are already in place across Europe today;
- determine policy actions at the EU level that foster the wider adoption of such best practices throughout the EU.

The group's work builds on the recognition that only an ambitious policy agenda developed in a multi-stakeholder setting involving both the EU and the Member States can bring about the quantum leap needed to address the unmet needs of people living with a rare disease today.

The OD Expert Group identified eight best practices addressing three key access challenges for OMPs and issued 15 calls to action for their swift adoption, see page 10 for an overview.

1. Bridge delays in the pricing and reimbursement processes

The first set of best practices addresses the need to bridge access delays caused by protracted P&R processes. The average waiting time for OMP availability in the EU is 542 days, well beyond the 180 days mandated in the Transparency Directive.[6] The positive impact of having early access to an OMP treatment on the lifespan of a person living with a rare disease can be immense. Any additional day that goes by between the point of marketing approval and the point of the reimbursement decision at the Member State level delays this positive impact.

Best practices. The OD Expert Group considers **early access solutions** as a best practice to bridge delays in the P&R process. These solutions enable the availability and financing of OMPs, providing patient access within three months from marketing approval.

One best practice example of an early access solution is the French Early Access Authorisation Autorisation d'Accès Précoce (AAP). The AAP provides access to innovative medicines that significantly benefit patients during the period between regulatory approval and P&R decisions. AAP applications are processed according to the established timelines with an average application time of 77 days, i.e. less than three months. The pricing agreement allows companies to set prices freely. A payback mechanism ensures that if the final negotiated price is lower than the price set for the AAP access, the manufacturer must pay back the difference. Such an early access solution ensures timely patient access.

(1) As reported on the EMA website [link]. (2) See Detiček et al. (2021) who documents inequality in access in the European countries. (3) European Commission. (2023). Reform of the EU pharmaceutical legislation. See [link]. (4) EP plenary vote on 10 April 2024, see [link]. (5) EFPIA (2023). (6) Council Directive 89/105/EEC relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of national health insurance systems.

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Call to action. To encourage the wider adoption of early access solutions, the OD Expert Group calls on the European Commission and Member States to take the following actions.

The European Commission should acknowledge the effectiveness of early access solutions in promoting timely access to OMPs and actively seek political commitment by **[1] issuing a recommendation to the European Council** and calling for their wider adoption of early access solutions across Member States.

In addition, **[2]** the European Commission should engage relevant stakeholders and build on existing platforms, such as meetings of the National Competent Authorities on Pricing and Reimbursement and Public Healthcare Payer, to **foster knowledge exchange on existing early access solutions** and to develop a **blueprint** for early access solutions to facilitate their implementation across Member States.

Finally, **[3]** to support the uptake of early access solutions among Member States, the European Commission should **provide funds for their implementation**. For example, the European Commission could define early access solutions as a priority area in the next EU4Health Annual Work Programme.

Early access solutions, however, should not be seen as a final solution, but as a bridge for immediate access for patients with unmet needs until the P&R process is concluded. The final solution must be for the P&R process to be concluded earlier and for more OMPs.

2. Speed up pricing and reimbursement processes and ensure successful outcomes

The second set of best practices addresses the need to reduce the time to reach P&R decisions and increase the likelihood of successful outcomes. One key challenge is that, due to small patient populations, it is often unfeasible to conduct large randomised controlled trials (RCTs) and provide evidence that yields robust results in line with standardised methods. Nearly three-quarters (70 per cent) of OMPs are approved based on data from a single pivotal clinical trial.[1] This limited clinical evidence complicates P&R processes, which typically require the robustness of evidence coming from RCTs to justify reimbursement decisions.

Moreover, differing ability to pay across Member States remains a major barrier to equitable access. In particular, companies face structural barriers to implementing differentiated pricing strategies such as external reference pricing (ERP) and parallel trade. As these policies do not allow effective price differentiation, access is often delayed in countries with lower ability to pay, and in some cases, companies withdraw OMPs altogether.

In recent years, companies, patient organisations and policymakers have proposed several solutions to enable pricing according to countries' ability to pay. The OD Expert Group would like to highlight three of these: equity-based tiered pricing, joint procurement, and an EU solidarity fund. While tiered pricing is the most developed proposal, the other two require further analysis. In particular, the impact of joint procurement on early and equitable access, including on industry competitiveness, has not been assessed, and the feasibility and design of the EU solidarity fund remain unclear.

The OD Expert Group has identified the following best practices and calls to action for managing uncertainty surrounding clinical effectiveness and enabling pricing according to the country's ability to pay.

2.1. Manage uncertainty surrounding clinical effectiveness

Best practices. The use of real-world evidence (RWE) in decision-making is recognised as a best practice for addressing evidence gaps due to insufficient evidence on the treatment efficacy generated through clinical trials. Integrating RWE into P&R decision-making can expedite the process and facilitate access. Examples of RWE use in decision-making can be found in France, the Netherlands and the UK.

Efficient RWE generation, however, depends on early alignment among payers, regulators and companies on data collection requirements. A one-size-fits-all approach is not feasible for rare and complex diseases, where evidence needs vary depending on the type of disease and patient population size. The **Mechanism of Coordinated Access (MoCA)** provides a multi-stakeholder forum to support such early alignment, constituting a best practice.

Finally, linking RWE to payments is essential when OMPs offer long-term benefits. In such cases, uncertainty around long-term effectiveness can hinder market access, despite the potential for significant improvements in quality of life for people living with a rare disease. The OD Expert Group finds that **performance-based managed entry agreements** (PBMEAs) are a best practice that helps to facilitate access in these situations.

Today, EU Member States still encounter many challenges across the production, acceptance and use of RWE in decision-making. The OD Expert Group therefore calls on the European Commission and Member States to tackle these challenges by taking the following actions:

(1) As reported on the EMA website [link]. (2) See Detiček et al. (2021) who documents inequality in access in the European countries. (3) see Article 71 in COM (2024) 193 final, see link and EP plenary vote on 10 April 2024, see [link]. (4) EFPIA (2023).

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Call to action. Policymakers should **[4] recognise RWE as a specific and valid source of clinical evidence**, also in the context of marketing authorisations. The OD Expert Group proposes to do this during revisions to Directive 2001/83 and the current Annex I. This inclusion will further support the role of RWE as a reliable source of evidence and remove the remaining barriers to using RWE in decision-making.

Furthermore, without delay, the European Commission should set up an Expert Group or Task Force to **[5]** establish common **standards for RWD collection and analysis**. The group should also set clear, specific standards tailored to the use of RWE to support marketing authorisation decisions and inform HTA assessments.

The **guidance on data collection, analysis, and using RWE for rare diseases** to ensure common acceptable standards. The Commission should also **[6] encourage using MoCA** as a starting point to discuss evidence needs.

In addition, to enable access to high-quality RWD, the European Commission should **[7] ensure that Multiannual Financial Framework funds are allocated to improve the quality and accessibility of real-world data (RWD)**.

While actions regarding RWE are feasible, addressing the ability to pay presents significant challenges, as it requires solidarity among Member States.

2.2. Enable pricing according to ability to pay

Best practices. The OD Expert Group recognises **tiered pricing** as a best practice that enables pricing according to a country's ability to pay. Many pharmaceutical companies already practice tiered pricing by setting different prices for the same treatment depending on a country's wealth, market conditions, or overall ability to pay. Their efforts, however, are limited by external reference pricing (ERP) policies and parallel trade, which further hinders access.

Some Member States have introduced policy measures to mitigate the impact of ERP. Denmark, for example, has recently introduced a three-year pilot allowing confidential price discounts. Also, Hungary and Germany are adjusting their pricing policies to mitigate the distorting effects of ERP. While these national reforms are steps in the right direction, a **more systematic EU-wide** approach is needed to solve countries' ability to pay as a remaining hurdle for equitable access.

Call to action. To enable pricing according to ability to pay, the OD Expert Group calls on the European Commission and Member States to take the following actions:

[8] Implement equity-based tiered pricing through a pilot programme for selected rare disease treatments. The pilot should be co-developed with broad stakeholder representation.

Furthermore, the European Commission should **[9] assess the impact of a joint procurement** on early and equitable access to OMPs and conduct a competitiveness check through a dedicated initiative.

Regarding an EU solidarity fund proposal, the European Commission should **[10] explore the use and feasibility of an EU solidarity fund** to incentivise earlier and more equitable access to OMPs. Such a fund has the potential to promote equitable access, while also incentivising timely engagement from both companies and payers.

Enabling pricing according to the ability to pay is not only about acting on big policy proposals. Removing structural barriers to the implementation of innovative contracting schemes, such as PBMEAs, is equally important. The OD Expert Group, therefore, calls on the European Commission to **[11] clarify EU accounting rules to promote access.**

The EU cannot stop when all Member States have timely P&R agreements in place because, in some situations, the treatments cannot yet be delivered to patients in each Member State at the point of marketing authorisation. This is the case when a Member State has insufficient infrastructure and/or specialised teams to administer the treatment.

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3. Enable effective access to cross-border healthcare

Innovative treatments, such as advanced therapy medicinal products (ATMPs), may modify or even cure (rare) diseases. Yet, people living with a rare disease may find that these highly innovative treatments are not available in their home country. This is partly because the rarity of the diseases in question – 88% of rare diseases affect fewer than 0.1 in 10,000 people[1] – makes it difficult for individual Member States to build and maintain the necessary expertise and infrastructure to deliver specialised care. Many lack the skills, technologies, and facilities to administer complex treatments. As a result, **many people living with rare diseases must seek care abroad**. In theory, the concentration of skills and resources to deliver certain treatment in some, instead of all, EU Member States would lead to a more efficient use of healthcare resources across the EU.

However, today, the existing EU framework for access to cross-border healthcare neither accommodates the needs of people living with a rare disease nor allows it to accommodate payments for innovative, disease-modifying and potentially curative therapies. Administrative, budgetary, and payment barriers restrict patient access to cross-border healthcare.

Best practices. The OD Expert Group has identified three best practices that enable effective access to cross-border healthcare:

A first best practice is **specialised expertise of the European Reference Networks (ERNs)** in complex, rare diseases and its use in cross-border advice on diagnosis and treatment. This collective knowledge helps clinicians across Europe manage rare diseases by tapping into a broader pool of experts. As a result, patients benefit from faster, more accurate diagnoses and access to optimal treatment plans, regardless of their country of residence.

Effective access to cross-border healthcare can be achieved outside the existing EU framework. The recognised second-best practice is bilateral agreements between domestic payers and foreign treatment centres. These agreements offer a practical and targeted solution to the administrative burden and financial barriers that often hinder access within the current EU framework. By allowing arrangements tailored to specific patient needs and institutional capabilities, they help ensure timely and appropriate care for patients requiring specialised treatment abroad.

Finally, the OD Expert Group recognises the potential of the recently suggested **backpack solution** in enabling effective access. This arrangement bypasses traditional cross-border pharmaceutical logistics, as the treatment is ordered and paid under the home country's P&R agreements but delivered and administered abroad.

Call to action. To ensure effective access to cross-border healthcare for people living with a rare disease, the OD Expert Group calls on the European Commission and Member States to take the following actions:

The European Commission should **[12] examine authorisation rules across Member States** to ensure they uphold patients' rights and avoid unnecessary demands for information. It should also use existing platforms to address current budgetary and payment barriers. These discussions should consider solutions within and outside the existing EU legal framework.

Furthermore, decision-makers should **[13] grant ERNs a legal mandate to serve as advisory experts** in the EU framework for access to cross-border healthcare. This advisory role of ERN should be prioritised and formally discussed within the framework of the Joint Action JARDIN under the EU for Health Programme, which seeks to integrate ERN activities into national healthcare systems.

Excessive restrictions on the free movement of people (patients) should be avoided. In this respect, the European Commission **[14]** should monitor and mitigate excessive restrictions on the free movement of persons.

Effective access is not only about having rules that are fit for purpose, but also about ensuring healthcare professionals are aware that they can use them and understand how to do so. The OD Expert Group, therefore, calls on the European Commission to **[14]** raise awareness among healthcare professionals about patients' rights to cross-border healthcare, to ensure that people living with rare diseases can access timely, specialised treatment not available in their home country.

The OD Expert Group calls on both the EU and national policymakers to act without delay

On the following pages, we describe best practices that promote early and equitable access and detail actions at the EU level needed to foster their adoption by the Member States. Best practices outlined in this report should be the guiding stars in policymakers' efforts to improve access to OMPs. The European Commission and national policymakers must act promptly to ensure the swift adoption of best practices outlined in this report.

(1) Bouwman et al. (2024).

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EARLY access because of unmet needs
EQUITABLE access regardless of socioeconomic status and place of residence

	Bridge delays in the pricing and reimbursement process	Speed up the pricing and reimbursement process and ensure successful outcomes		Enable effective access to cross-border healthcare
		Manage uncertainty surrounding clinical effectiveness	Enable pricing according to ability to pay	
Needs				
Best Practices	• **Early access solutions**, such as the Early Access Authorisation in France, facilitate access before the pricing and reimbursement process is finalised • Key design features include free price setting at launch, a payback mechanism, and a dispute resolution mechanism	• **The use of RWE in P&R decisions** with examples from France, the Netherlands, Scotland and the UK • **Early dialogue** on the evidence requirements as offered by MoCA • Linking RWE to payments using **PBMEAs**	• **Tiered pricing** is a pricing strategy in which a company sets different prices for the same product in different markets, based on their ability to pay	• **Specialised expertise** of ERNs in complex, rare diseases and their cross-border operations • **Bilateral agreements** between Member States regulating access to very specialised care • **Proposal for a backpack solution**
Call to Action	1. **Generate political commitment** by proposing a recommendation to the European Council on the adoption of early access solutions 2. **Promote early access solutions** among Member States and support them in developing **a blueprint solution** for implementation 3. **Provide financial support for the implementation** of early access solutions	4. **Recognise RWE as a specific and valid source of clinical trial evidence** in the revised general pharmaceutical legislation 5. **Align standards** on RWD collection, analysis and use of RWE in decision-making 6. **Promote MoCA** and ensure adequate financial support for its operations 7. **Invest in the digital infrastructure** to ensure the availability of high-quality RWD	8. **Implement equity-based tiered pricing through a pilot** programme for selected disease treatments 9. **Assess the impact of joint procurement** on early and equitable access to OMPs and industry competitiveness 10. **Explore the design and feasibility of an EU solidarity fund** 11. **Clarify EU accounting rules to promote access**	12. **Improve the authorisation process and address budgetary and payment barriers** in cross-border healthcare 13. **Grant ERNs a legal mandate to perform an advisory role** in access to cross-border healthcare 14. **Monitor and mitigate excessive restrictions** on the free movement of persons 15. **Raise awareness** about access to cross-border healthcare

The OD Expert Group urges the European Commission to act on the calls without delay.

1
BRIDGE DELAYS IN PRICING AND REIMBURSEMENT PROCESSES

Slow pricing and reimbursement processes delay patient access

Once an orphan medicinal product (OMP) is approved in the European Union (EU), it should be available without delay to people with rare diseases. However, this is not the case today. **Patients face significant access delays** due to slow and prolonged pricing and reimbursement (P&R) processes in their respective Member States.

A medicinal product can only be prescribed and reimbursed within the healthcare system once its price has been negotiated and officially established. Before the medical product is approved in the EU, patients may access treatments through clinical trials or, in exceptional cases, via compassionate use or early access programmes, see Box 1. However, after an OMP receives EU marketing approval, they must typically wait for the completion of the P&R process, which includes a Health Technology Assessment (HTA), before accessing the treatment.

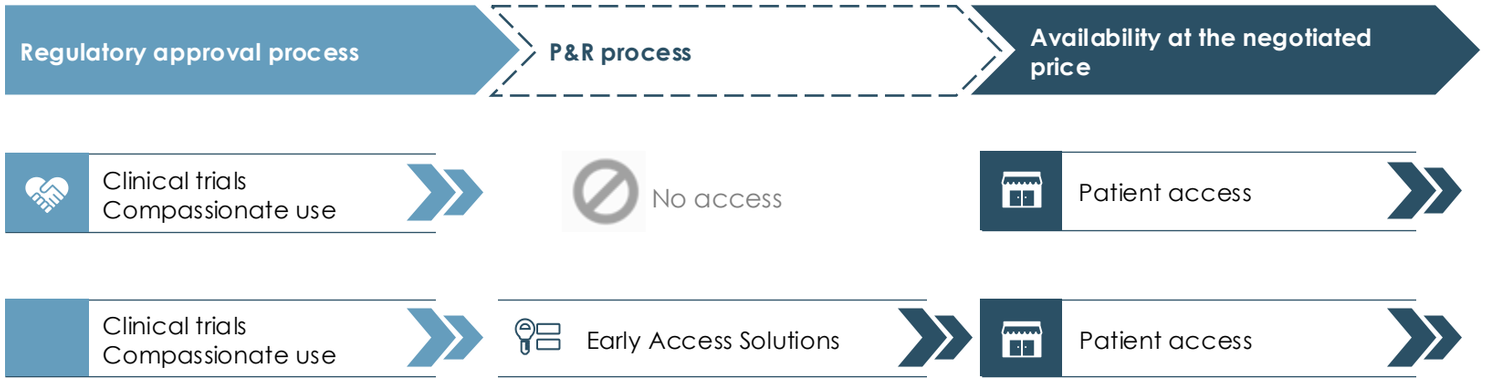
The **average waiting time for OMP access in the EU is 542 days,** approximately a year and a half, after receiving EU market approval.[1] This is well beyond the timeline mandated in the Transparency Directive,[2] which requires EU Member States to complete pricing and reimbursement decisions within 180 days to ensure timely access to medicines. **Several factors contribute** to delays in P&R processes.

First, the **initiation of negotiations can be delayed**, particularly when national payers rely on external reference pricing (ERP). ERP is a pricing strategy where a country sets the price of a medicinal product based on the prices in other countries. This means that if a country uses ERP, it may need to wait for pricing decisions in reference countries before starting its negotiations. As a result, the P&R process may only begin once other Member States have successfully completed their P&R negotiations.

Second, **the length of the P&R process varies significantly across countries**, and this variation is explained by multiple factors. These include clock stops, which are temporary pauses in the formal assessment timeline when national authorities request additional information from the manufacturer. These requests may involve additional clinical data, economic analyses, or clarifications of the product's value. The P&R process remains on hold until the requested information is provided. Additionally, misalignment concerning evidence requirements during the HTA process can result in rejections or repeated assessments. These factors add to access delays.

A best practice identified by the OD Expert Group is to use **early access solutions** to bridge the delays caused by slow P&R processes. These solutions enable early availability and financing of authorised medicinal products immediately after they receive marketing approval, but before the P&R decision, see Figure 1.

Figure 1. Early Access Solutions build an access bridge during the P&R process



Source: Copenhagen Economics.

Box 1. Access under compassionate use programmes

Compassionate use programmes (CUPs) provide an early access pathway to medicinal products that are not yet approved in the EU. They are intended for patients with severe or life-threatening conditions for whom satisfactory treatment is not currently available or who cannot participate in clinical trials. CUPs provide access to either a group of patients (also called a cohort) or to a named patient.

It is up to the Member States to decide which treatment should be considered and which patient group should be enrolled. There are substantial differences across countries concerning CUP design, approval process, liability, data collection, medicine supply, import process and payments.

Source: Polak et al. (2022a), EFPIA (2016), Schwinn et al. (2021)

(1) EFPIA Patient W.A.I.T. Indicator 2023 Survey [link]. (2) Council Directive 89/105/EEC relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of national health insurance systems.

Early access solutions are a best practice to bridge pricing and reimbursement delays

The OD Expert Group **recognises the early access solutions currently in place in France and Germany as best practice**, as they enable access within three months of submitting an (early access) application. Both solutions have clearly defined procedural timelines and price-setting mechanisms. However, they differ in eligibility criteria and coverage.

French Early Access Authorisation (AAP)

The French Early Access Authorisation (Autorisation d'Accès Précoce - AAP) facilitates early access to innovative medicinal products that significantly benefit patients, have a robust development plan, show promising clinical results, and address unmet needs. Such eligibility criteria are well-suited to accommodate OMPs.

The AAP has three distinct features that foster early access:

- *Clearly defined procedural timelines:* Applications are processed within three months of submission. This recognises the urgency of providing access to patients with unmet needs while accounting for safety requirements.[1]
- *Free price setting combined with a payback mechanism:* The payment for the AAP-eligible medicine balances the company's need to be compensated immediately while maintaining the possibility of price negotiations. The manufacturer can freely set the price for the entire programme duration. A payback mechanism ensures that if the final negotiated price is lower than the price set for the AAP access, the manufacturer must pay back the difference.
- *Coverage:* AAP allows the use of an innovative medicinal product for which the manufacturer agrees to apply for marketing authorisation or, if already authorised, to submit a request for P&R. Furthermore, similar to compassionate use programmes, access is limited to people living with severe or life-threatening conditions with unmet needs.

The AAP has been successful in providing early access to OMPs in France. Between 2018 and 2023, 221 medicinal products were included in the AAP, 20 per cent of which were OMPs. These OMPs represent 39 per cent of all OMPs approved in the EU over the same period.[2] Furthermore, AAP applications are processed according to the established timelines, with an average application period lasting 77 days (less than three months), ensuring timely patient access.

German Automatic Reimbursement Framework

In addition to France, the Automatic Reimbursement Framework in Germany offers an early access solution whereby new medicinal products can be marketed directly after the approval of a medicinal product. The system has the following key characteristics:

- *Immediate reimbursement eligibility:* Once approved, new/innovative medicines are immediately eligible for reimbursement from the statutory health insurance funds.
- *Free price setting for a limited period combined with a payback mechanism:* The manufacturer can freely set the price for six months after market launch. During this period, the German Federal Joint Committee (G-BA) evaluates the medicinal product to determine its additional benefit for the patient compared to an appropriate comparator therapy and assigns a score indicating such benefit.[4] If the final negotiated price is lower than the initial free price, manufacturers must reimburse the difference.
- *Arbitration board:* In the absence of an agreement, an arbitration board sets a final, legally binding price. Manufacturers must accept such a price or withdraw the medicinal product from the market.
- *Coverage:* Unlike the French AAP, the German solution covers all innovative medicinal products approved in the EU, regardless of whether they address an unmet need.

The Automatic Reimbursement Framework is efficient in providing early access. It takes 96 days on average for OMP products to gain access to the reimbursement list.[5]

If more EU Member States adopted early access solutions like those currently applied in France and Germany, the waiting time for people living with a rare disease to access OMPs would be significantly reduced. These frameworks enable timely access to innovative OMPs while ensuring that national health systems retain control over pricing and reimbursement negotiations. Expanding these best practices across EU Member States would help address long delays in access to life-saving treatments like OMPs.

(1) All medicines are assessed by HAS (French National Authority for Health) to ensure that safety is strongly presumed basedon the results of clinical trials. (2) Copenhagen Economics based on HAS data [link] and Orphanet Orphan Drug database data. This is a conservative estimate, as we match OMP authorisations and EAA decisions over the same period. (3) HAS (2023). See [link]. (4) For OMPs with an annual revenue threshold below EUR 30 million, their added benefit is assumed, and only the degree of additional benefit must be proven. (5) EFPIA Patient W.A.I.T. Indicator 2023 Survey [link].

Call to Action

Bridge delays in the pricing and reimbursement process

Early access solutions can effectively provide timely access to OMPs and may speed up access significantly. To encourage the wider adoption and implementation of these solutions across all EU Member States, the OD Expert Group calls on the European Commission and Member States to take the folowing actions.

1. Generate political commitment by proposing a recommendation to the European Council on the adoption of early access solutions

- The European Commission should acknowledge the effectiveness of early access solutions in promoting timely access to OMPs and actively seek political commitment to implement these solutions in all Member States.
- Specifically, the European Commission should propose a recommendation to the European Council to ensure the adoption of early access solutions across the EU.
- Such political commitment at the EU level is crucial for driving changes at the national level.[1]

2. Promote early access solutions among Member States and develop a blueprint solution for implementation

- The European Commission should facilitate exchanges between Member States regarding experiences and insights on early access solutions. This would help national decision-makers understand the benefits and challenges of this solution. To support such exchanges, the European Commission should leverage existing platforms such as meetings of the National Competent Authorities on Pricing and Reimbursement and Public Healthcare Payers (NCAPR), the Safe and Timely Access to Medicines for Patients (STAMP) group, or the Pharmaceutical Committee.
- Over time, the platform could refine early access solutions into a blueprint that balances the needs of all stakeholders. This could include safeguards to prevent payers and companies from being pressured into pricing decisions and introduce independent mediation to resolve disputes. A blueprint would facilitate the uptake of early access solutions by Member States while incentivising pharmaceutical companies to use them.

3. Provide financial support for the implementation of early access solutions

- The European Commission should support Member States in adopting early access solutions by providing funds for their implementation. As part of the implementation, the support should cover training and resources to strengthen the capabilities of staff involved in pricing, reimbursement, and regulatory processes.
- For example, the European Commission could define early access solutions as a priority area in the next EU4Health Annual Work Programme.

(1) In 2003, the Council of Ministers recommended systematic population-based screening, supported by guidelines and a Europe-wide campaign. The introduction of breast cancer screening in 2005 and 2007 increased coverage, early detection, and reduced late-stage cancer incidence and mortality. Source: Evaluation of Mammography Screening Programme in Germany. See link.

2
SPEED UP THE PRICING AND REIMBURSEMENT PROCESSES AND ENSURE SUCCESSFUL OUTCOMES

Limited clinical evidence creates challenges for P&R processes

Uncertainty around clinical effectiveness is inherent to rare and complex diseases with small patient populations

Uncertainty around clinical effectiveness is inherent to rare diseases due to small populations. Only 4 per cent of rare diseases have a prevalence rate of one to five in 10,000, while as many as 88 per cent affect fewer than 0.1 in 10,000 people.[1] As a consequence, evidence on efficacy is often limited at the point of marketing authorisation and does not meet the standards set by randomised controlled trials (RCT), which are considered the gold standard in clinical effectiveness assessment. Notably, 70 per cent of OMPs approved between 2010 and 2022 were approved based on data generated in just one pivotal clinical trial.[2]

Furthermore, 33 per cent of OMPs are subject to nonstandard marketing authorisations, see Figure 2. In turn, 21 per cent receive a conditional marketing authorisation requiring limited initial data to be supplemented by additional evidence collected through post-marketing authorisation studies. The remaining 12 per cent receive authorisation under exceptional circumstances; this refers to situations where a collection of comprehensive safety and efficacy data is not possible due to ethical or practical constraints. Data are limited, and so is the ability to reach statistical thresholds of effectiveness established by RCTs.

Limited evidence on effectiveness presents a challenge for effective P&R processes

Limited clinical evidence on the effectiveness of the treatment does not allow fully informed P&R decisions. For example, in Germany, OMPs face the same standard of robust evidence required for non-orphan medicinal products if their annual revenue exceeds EUR 30 million.[3] The results of the German Federal Joint Committee's (G-BA) decisions on OMPs show that in 32 per cent of cases, the additional benefit, a measure of its value to inform pricing decisions, was not quantifiable due to the lack of scientific data, see Figure 3.

Furthermore, healthcare authorities and payers frequently express concerns regarding the clinical evidence on the effectiveness and cost-effectiveness of therapies in cases where the gold standard of RCT cannot be reached.[4] This often leads to lengthy dossier evaluation and makes price negotiations difficult. For example, it took two years for the National Institute for Health and Care Excellence (NICE) to reach a reimbursement decision on second-line therapy for people living with sickle cell disease (SCD).[5]

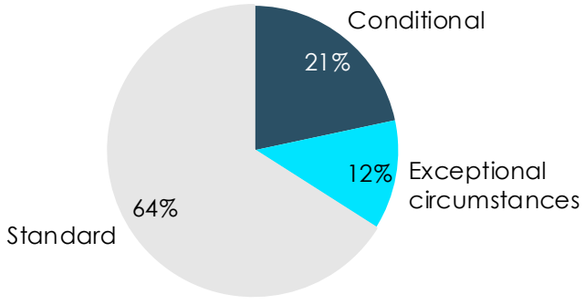
The OD Expert Group has identified three best practices that address challenges related to limited clinical evidence and can make the P&R process more efficient. These include:

- accepting RWE to fill the gaps in evidence coming from clinical trials;
- ensuring early alignment on the scope of evidence required;
- linking RWE to payments in cases where treatments provide long-term benefits.

The following pages provide a detailed overview of these best practices, including examples.

Figure 2. Distribution of marketing authorisation types for OMPs

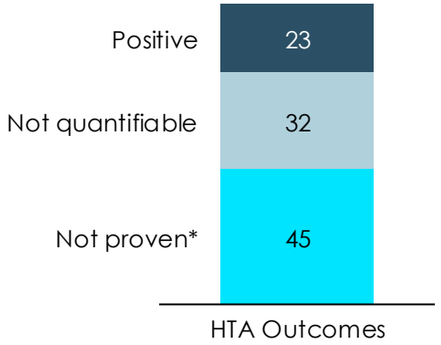
Per cent share



Note: Based on 192 OMPs approved between 2010 and 2022.
Source: Bowman et al. (2024).

Figure 3. Outcomes of German HTA assessments

Per cent of treatments assessed



Note: The category "Positive" is the sum of the benefit assessment categories minor (16), considerable (23), and major (2) (*) according to the strict evidence and methodological requirements prevalent in Germany.
Source: Copenhagen Economics based on Orphanet and GB-A assessments.

(1) Copenhagen Economics based on Orphanet data. (2) Bowman et al. (2024). (3) According to de Pouvourville et al. (2023), inGermany, evidence from randomised controlled trials remains the gold standard, and evidence based on RWD is generally rejected. (4) OD Expert Group(2023). (5) The treatment in question (Voxelotor) received marketing authorisation in February 2022 (see link). NHS approved the roll-out in 2024 (see link).

Accepting RWE is a best practice to fill evidence gaps for OMPs

RWE complements information collected in clinical trials

RWE describes the clinical evidence regarding the usage and the potential risks and benefits of a medical product derived from RWD analysis, that is, data collected from various sources outside of highly controlled clinical trials. RWD can come from different sources, including patient health records, administrative records, patient registries, surveys, observational cohort studies, and digital health technologies.

RWE can support regulatory and P&R decisions by providing complementary information that might be hard or impossible to gather from clinical trials, which is frequent in the case of rare diseases.

For RWE to be acceptable for decision-making, the data must come from reliable sources, be of high quality, and be relevant to the research question. Evidence should be generated in a scientifically rigorous and transparent way, using analytical methods that minimise potential bias and uncertainty.[1]

Several countries already use RWE to inform P&R decisions

While RWE is being increasingly used by the European Medicines Agency (EMA) to support decisions on approving new medicinal products or on extending the approved use of an existing medicine for new indications, age groups, or dosages, the use of RWE in the national P&R decisions remains limited.

Nevertheless, some European countries have demonstrated that RWE can be effectively integrated into decision-making for P&R. Importantly, across these countries, the collection of RWD happens as early as possible, namely during early access solutions implemented in these countries:

Orphan Drug and DRUG Access Protocols in the Netherlands

Launched in 2022, the pilot for the Orphan Drug Access Protocol (ODAP) incorporates a phased approach where RWE is systematically collected during early patient access to OMPs. Specialised hospital-based centres establish registries and conduct evaluations, ensuring that reimbursement and access decisions are based on robust clinical data from routine clinical practice.[2] The ODAP follows the DRUG Access Protocol, launched in 2021, which aims to provide access to innovative anti-cancer treatments that have shown positive results in clinical trials but are still awaiting marketing authorisation or reimbursement.[3]

Early Access Authorisation (AAP) in France

In the French AAP, described in Chapter 1, comprehensive data are collected through the *Protocole d'Utilisation Térapeutique* to support the product value proposition during the appraisal for reimbursement. It does not replace the standard clinical trials required for the marketing authorisation.

Ultra-Orphan Pathway in Scotland

The Scottish Ultra-Orphan Pathway supports pharmaceutical companies in making medicines available through the National Health Service (NHS) for an initial three-year period. During this period, further data are collected on the medicine's efficacy and used to inform P&R decisions.[4] The government provides guidance on evidence generation.

Early Access to Medicines Scheme (EAMS) in the UK

Established in 2014, the Early Access to Medicines Scheme (EAMS) enables UK patients with life-threatening or seriously debilitating conditions to access medicines awaiting marketing authorisation, where there is a clear unmet need. The scheme supports the generation of RWE, which has been used in over one in five appraisals by the National Institute for Health and Care Excellence (NICE), the health technology assessment body in England and Wales. The case study on ipilimumab highlights how using RWE can complement limited clinical evidence, see Box 2.

Box 2. Use of RWE led to a decreased cost

Case study of ipilimumab

In 2011, ipilimumab, a novel treatment for advanced skin cancer, received approval based on a clinical trial involving 676 patients. However, with only 55 patients from the UK participating in the trial, the NHS faced challenges in estimating the real-world utilisation of the drug, specifically the number of vials needed per patient (and thus the cost of treatment), which is based on body weight.

To address this challenge, at the reimbursement stage, RWE from an early access programme (EAMS) was used. Data from 258 UK patients receiving the drug through this programme were pooled with the clinical trial data. This revealed a significant difference in vial usage, with early access patients requiring an average of 1.19 vials per 50 mg dose compared to 1.51 vials in the clinical trial. Therefore, including early access data led to a decrease in mean cost estimates.

By using data from early access programmes, policymakers can better understand the real-world impact of new treatments, including their utilisation and cost-effectiveness.

Source: Polak et al. (2022b)

(1) These are the three high-level principles put forward in the NICE RWE framework. See [link]. (2) See [link]. (3) Zeverijn et al. (2022). (4) Scottish Medicines Consortium, Ultra-orphan medicines for extremely rare conditions. See [link]. (5) Polak et al. (2022b).

2.1. Manage uncertainty surrounding clinical effectiveness

Ensuring early alignment on the evidence required is key to speeding up P&R processes

Lack of consensus around evidence generation delays patient access

Today, developers face uncertainty about the evidence on efficacy that will be accepted for both regulatory approval and P&R decisions. The greatest challenge lies in the lack of consensus among developers, physicians, and regulators on what evidence should be collected and the criteria it must meet. In particular, regulators and national payers have differing requirements for RWE. While the EMA may accept certain types of RWD to support regulatory decisions, national payers often demand more stringent evidence to justify P&R decisions. As a result, evidence sufficient for regulatory approval may still be insufficient for market access, creating further delays and uncertainty in patient access to treatment.

The lack of consensus around evidence generation leads to inefficiencies, affecting both clinical and non-clinical data collection. As a result, developers may produce data that does not fully meet the expectations of regulators or payers, leading to further rounds of evidence generation and review, causing delays in patient access to new treatments. There is, therefore, a need for early alignment on evidence expectations and value measures across stakeholders.

MoCA supports early structured discussions around the type of evidence required

Early dialogues allow stakeholders to align on expectations regarding what types of data need to be collected to document efficacy. A best practice in this respect is MoCA, established in 2013. MoCA is a voluntary, non-legislative, and non-binding setting where people living with a rare disease, company representatives, regulators, representatives of HTA and payer bodies can exchange information to examine the value of an OMP.

A recent evaluation points to the following benefits of MoCA[1]:

- *Meaningful engagement of people living with a rare disease:* Their engagement fosters a better understanding and addressing of unmet needs, disease burden, and treatment value. The importance of such engagement in the decision is highlighted in the Rare 2023 Foresight Study.[2]
- *Identification of evidence gaps:* Early dialogue between stakeholders helps identify and address evidence gaps upfront, supporting an efficient P&R process. In complex diseases affecting small patient populations, evidence gaps are inevitable and can be addressed with RWE.
- *Multi-stakeholder alignment:* MoCA allows a coordinated interaction with multiple agencies, competent authorities and representatives of people living with a rare disease. This collaborative approach helps optimise study design and data collection, enhancing the relevance of evidence and allowing better cost predictability at the same time. It ensures that evidence generation is efficient, streamlined, and aligned with regulatory and payer expectations. Such alignment is especially valuable for cost-constrained small and medium-sized enterprises (SMEs).
- *Transparent value assessment framework:* Trust and mutual understanding are built between payers and developers through a structured dialogue supported by a transparent value assessment framework.

Over the past decade, MoCA has proven to be a valuable platform for early dialogue and multi-stakeholder collaboration in the OMP landscape. With 47 meetings held to discuss 23 different OMPs,[3] MoCA has successfully fostered patient engagement, built trust between payers and developers, and promoted equitable access to innovative therapies among people living with a rare disease across Europe. By facilitating informed decision-making through a transparent value assessment framework, MoCA contributes to the efficient and effective development and accessibility of OMPs.

Greater commitment and assessment alignment are needed for effective implementation

Deploying MoCA is, however, not without challenges. These include:

- *Voluntary and non-binding nature:* Since participation is voluntary and outcomes are not legally enforceable, stakeholders may lack strong incentives to engage fully or adhere to agreements. This can lead to inconsistencies in implementation and reluctance from payers and developers to participate. Additionally, without binding commitments, the process may lack predictability, reducing its effectiveness in facilitating timely access to OMPs.
- *Resource constraints:* Limited financial and human resources among stakeholders, on the regulatory and payer bodies' side in particular, can impede their active participation and the sustainability of coordinated efforts.
- *Data sharing limitations:* Challenges related to data privacy, standardisation, and interoperability restrict the effective sharing of information necessary for coordinated assessments.
- *Inconsistency in the HTA value assessment:* Variations in clinical thresholds, economic evaluations, and ethical considerations and different levels of reliance on RWE create challenges for alignment, making it difficult to generate recommendations accepted across jurisdictions. [4]

While MoCA supports structured discussion about the type of evidence required, its effective implementation and broader uptake require greater stakeholder commitment and convergence in assessment methodologies.

(1) See Cavaller-Bellaubi et al. (2023). (2) Recommendations 5 and 8 of the Rare 2030 Foresight Study (link). (3) ibidem, (4) See, for example, Bell et al. (2023).

Managing uncertainty around long-term benefits requires linking RWE to payments

Uncertainty about the long-term effectiveness of disease-modifying and potentially curative treatments poses access challenges

Disease-modifying and potentially curative treatments, such as precision medicine or ATMPs, are anticipated to replace lifelong treatments or care. They are designed to have therapeutic effects lasting for years but are often administered only once or a few times in a short period. The uncertainty about the long-term outcomes of such treatments poses challenges to market access.[1,2]

Several additional factors complicate the design and evaluation of these treatments: low disease prevalence (often limited to a few patients), severity and burden of the diseases, limited availability or lack of authorised treatments, heterogeneity within the patient population, or the significant presence of paediatric patients.[3] Furthermore, using a placebo comparator in the clinical trial may be considered unethical, raising dilemmas around the RCT design. Pivotal studies for approved ATMPs are typically small, open-label, non-randomised and often lack control groups or use historical controls. Intermediate or single variables are commonly used to assess the efficacy of the treatment. Consequently, the submitted data frequently fall short of meeting the clinical evidence standards applied to other submissions for biological medicinal products.

Linking the collection of RWE to payments can speed up and increase the chances of patient access in such cases

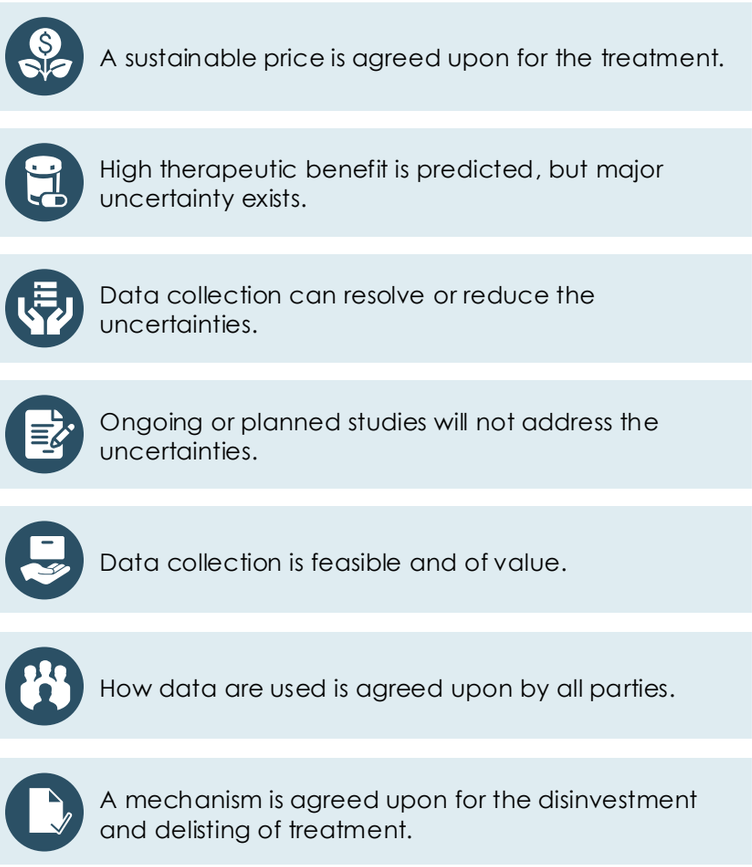
On the one hand, these transformative therapies offer the potential to significantly improve the quality of life of people living with a rare disease. On the other hand, they often come with high uncertainty about their long-term effectiveness and high costs that may not be sustainable for payers and society. Of the 12 ATMPs approved as of March 2022, 11 are designed to be administered as a single, one-off treatment.[4]

The OD Expert Group considers the use of PBMEAs as a best practice solution to address this dilemma.[5] Such agreements link the reimbursement of treatment to its actual performance in real-world settings. PBMEAs can increase access to OMPs with long-term, disease-modifying, and potentially curative effects while ensuring value for money and reducing financial risk. These agreements are concluded between the marketing authorisation holder and the payer, with the involvement of expert physicians and/or people living with a rare disease. Incorporating patient-centric metrics in such agreements ensures patients' engagement and facilitates data collection, supporting more informed decision-making. Three selected examples of such agreements are presented on the next page.

Implementing PBMEAs, however, is challenging and requires defining appropriate outcomes and collecting relevant data, risks and benefits sharing between stakeholders.[6] *Impact HTA* has developed a checklist to determine whether the PBMEA is recommended, given its high negotiation and implementation costs, see Figure 4. Using such a checklist is also considered a best practice.

Finally, PBMEAs are currently being discussed within the framework of the WHO/Europe Access to Novel Medicines Platform. Its working group on sustainability is exploring what financial arrangements can be put in place to manage uncertainties around managed entry agreements.[7] The recommendations resulting from this project should be implemented in the Member States and endorsed by the European Commission.

Figure 4. Checklist for the use of PBMEAs



Source: Impact HTA: Checklist for rare disease treatments. See link.

(1) Disease-modifying refers to acting directly on the disease causes. (2) ATMPs include products derived from genes, tissues, or cells. (3) See Iglesias-Lopez et al. (2021) or TLV (2021). (4) Wilkins et al. (2023). (5) Managed Entry Agreements (MEA) are contractual arrangements between payers and developers that allow new medicines to be covered under healthcare budgets while managing uncertainty around their financial impact or performance. Performance MEAs link coverage and payments to medicinal product performance. The number of MEAs is relatively small in most countries. See Wenzl and Chapman (2019). (6) Facey et al. (2021). (7) Access to Novel Medicines Platform: Meeting of Working Group 3 on Sustainability, see [link].

Examples of performance-based agreements for ATMPs

Haemophilia A

Case study

ROCTAVIAN® (valoctocogene roxaparvovec) is a gene therapy designed to treat severe haemophilia A, a genetic disorder affecting clotting ability. Although promising, the one-off cost of this therapy can create barriers to payer acceptance due to budget constraints relative to the current standard of care. Delivered as a single-dose intravenous infusion over 3 to 4 hours, the therapy costs approximately USD 900,000 per patient, according to the list price.

BioMann, the company that developed ROCTAVIAN®, addressed these challenges by reaching an agreement with the German National Association of Statutory Health Insurance Funds on an outcome-based prospective cohort model for the treatment.

Future reimbursement will be increased or decreased based on the RWE on the efficacy of the treatment. Data are being collected by the German Haemophilia Registry of patients. The agreement was concluded with a minimum term of three years to ensure security of supply and reimbursement.

In addition to the GKV-SV agreement, BioMarin has also agreed rebate contracts with some Statutory Health Insurance umbrella organisations.

Source: BioMarin Pharmaceuticals (2023). See link.

CAR-T cell therapies

Case study

In 2018, two CAR-T cell therapies were approved for cancer treatment. These therapies offered the potential for transformative benefits but posed significant challenges for HTA bodies and payers. Key concerns included uncertainty about the therapies' long-term value in real-world settings due to limited data at launch, coupled with their high upfront costs.

To address these challenges, innovative payment models were developed and successfully implemented in several EU Member States. These agreements between payers and developers focused on two key elements: outcome monitoring and evidence generation.

For example, in France, annual reassessments were conducted based on longer-term follow-up data from pivotal trials and included post-launch data collection.

Source: Jørgensen et al. (2020).

Crohn's disease

Case study

Crohn's disease is a chronic inflammatory bowel disease that can lead to a range of complications. In 2018, the first centrally approved autologous cell therapy was approved in the EU.

To address payer concerns about individual patient outcomes, Takeda introduced a pay-for-performance model to align payment with treatment success. This model divides the payment into two distinct instalments:

- Prescription-linked payment: The first instalment is paid when the treatment is initially prescribed, ensuring immediate patient access.
- Outcome-linked payment: The second instalment is paid only if the patient achieves full remission, as confirmed by the treating clinician through MRI scans. This ensures that payment is directly tied to demonstrable clinical benefit.

By reducing reimbursement barriers, this approach helped improve patient access to treatment while addressing payer concerns about effectiveness.

Source: Copenhagen Economics (2023).

A remaining barrier is the limited infrastructure to produce high quality data

In recent years, the EU has put forward two initiatives to improve access, analysis, and use of RWE in decision-making. These initiatives include:

- *European Health Data Space - EHDS:* The EHDS is a common framework proposed by the European Commission in 2022 that promotes better exchange and access to different types of health data.[1] This includes access to secondary health data, or RWD, which is a valuable source when conducting RWE studies.
- *Data Analysis and Real-World Interrogation Network – DARWIN EU:* Established in 2022 at the EMA, DARWIN EU aims to support the decision-making process by establishing and expanding a catalogue of observational data sources and addressing questions regarding the use of these data in studies.[2] One of its first disease epidemiology studies investigated the prevalence of rare blood cancers in five European countries.[3] By 2025, DARWIN EU will be fully operational, delivering around 150 RWE studies per year.

However, three barriers at the national level limit the use of RWD and RWE in decision-making: concerns about the quality and limited digital infrastructure to provide such data.

Concerns about the quality

First, although national HTA bodies and payers recognise the limited evidence from clinical trials for rare diseases, they doubt whether RWD can provide high-quality evidence for assessing treatment effectiveness.

This concern is manifested through the implementation of the EU Regulation on Health Technology Assessment (EU HTA), which provides a framework and rules to perform HTA jointly at the EU level. [4] On the one hand, Recital 24 of the Regulation explicitly recognises the challenges and calls to adopt methodologies of joint clinical assessment and joint clinical consultations to reflect the specificities of treatments for rare diseases. On the other hand, the initial EU guidance on direct and indirect comparisons prioritises the use of RCTs and dismisses RWE and single-arm trials as insufficient.[5]

If this situation continues, it will inevitably lead to a longer assessment process, not addressing evidence gaps, and consequently, increasing the probability of unsuccessful P&R negotiations.

Barriers to accessing and sharing patient registry data

Second, rare disease patient registries hold critical potential for generating RWE, but their use is severely limited by fragmentation and lack of interoperability. Today, the EU has 845 different rare disease registries, cohorts, and databases.[6] Registries of patients treated with OMPs are particularly relevant as they allow the gathering of evidence on the safety and effectiveness of the treatment. Using them, however, is difficult for the following reasons:[7]

- *Heterogeneous approaches:* Different countries and regions use various methods and structures for their registries, which makes combining data across countries difficult.
- *Data fragmentation:* Rare disease patient data are often spread across numerous registries, leading to serious fragmentation. This makes it challenging to gather comprehensive datasets for a specific rare disease.
- *Interoperability:* Achieving interoperability between different registries and other health data systems is a major challenge.
- *Data collected on project-based funding:* Many registries rely on project-based funding, which is inherently precarious and does not guarantee long-term operation and maintenance.
- *Legal and ethical issues:* Some registries may lack the robust health data governance frameworks that are needed for sharing patient health data. Issues such as informed patient consent, privacy, and data protection are complex and need clear accountability mechanisms.

EU-funded research projects, such as the European Joint Programme on Rare Diseases (EJP RD) and the European Rare Diseases Research Alliance (ERDERA), aim to create a network of rare disease resources, including patient registries. While these projects develop harmonised approaches and provide a platform for data sharing, it is the responsibility of the owners of patient data to invest in data quality and robust governance structure and digital infrastructure to ensure their data are FAIR and ready for secondary use.

Finally, controversy remains around capturing data from compassionate use, with some countries prohibiting data collection through such programmes. For example, in Belgium, only data supporting the programme's evaluation can be collected. In Austria, data collection is prohibited in a named-patient setting.[8]

(1) European Commission on European Health Data Space. See link. (2) European Medicines Agency on DARWIN EU. See link. (3) DARWIN EU, Prevalence of rare blood cancers in Europe. See link. (4) Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment. See link. (5) EU HTA Coordination Group, Methodological & al Guidelines for Quantitative Evidence Synthesis: Direct and Indirect Comparisons, adopted 8 March 2024. (6) Orphanet Report Series – Rare Disease Registers, cohorts and database – April. (7) For details, see Rare 2023 – Foresight in Rare Disease Policy: Rare Disease Data Collection and Utilisation. See link. (8) Polak et al. (2022a).

Call to Action

Manage uncertainty surrounding clinical effectiveness

RWE is key to addressing evidence gaps due to insufficient efficacy data generated through clinical trials in small patient populations. Integrating RWE in decision-making processes can significantly expedite P&R decisions in such cases. However, many challenges remain across the EU in the production, acceptance, and use of RWE in decision-making. To promote the use of RWE in decision-making, the OD Expert Group calls on the European Commission and Member States to take the following actions:

4. Recognise RWE as a specific and valid source of clinical trial evidence in the revised general pharmaceutical legislation

- Policymakers should recognise RWE as a specific source of clinical evidence, also in the context of marketing authorisations. This can be done during revisions to Directive 2001/83 and the current Annex I. This inclusion will further support the role of RWE as a reliable source of evidence and help to remove remaining barriers[1] to the use of RWE in decision-making.
- To achieve this, it is essential to expand the wording of the legislation to include reference to RWE. The revised wording should acknowledge that RWE can fill the evidence gaps and should cover both pre- and post-approval data. Accompanying guidance should also reference high-level principles to inform the collection and analysis of RWD. This will provide a clear signal for unlocking the use of RWD and RWE in decision-making.

5. Align standards on RWD collection, analysis and use of RWE in decision-making

- Without delay, the European Commission should set up an Expert Group or Task Force to establish common standards for RWD collection and analysis. The group should also set clear, specific standards tailored to the use of RWE to support marketing authorisation decisions and inform HTA assessments, recognising the differing evidentiary needs and objectives of each process.
- Such a group should include members of the DARWIN EU network, RWE4Decisions, and ERNs, with support from countries where such data are used or where the guidelines or data protocols exist, such as the Netherlands, France, or the UK.
- RWD standards should build on terms and definitions put forward in the recent ICH Guideline.[2]

6. Promote the MoCA initiative and ensure adequate financial support for its ongoing operations

- The European Commission should increase awareness of MoCA among stakeholders and encourage its use as a starting point for discussions on evidence needs.
- The European Commission should allocate funding to support the MoCA secretariat and ensure its effective functioning as an independent facilitator.
- Member States should support MoCA and ensure payers' participation in its meetings.

7. Invest in the digital infrastructure to ensure availability of high-quality data

- Policymakers must ensure that the Multiannual Financial Framework (MFF) funds are allocated to improve the quality and accessibility of RWD collected through patient registries. At a minimum, the data collection and sharing capacity of European Reference Networks must be ensured.
- The funding should cover investments in the following activities:
  - Standardised data collection – to ensure consistency and comparability across registers
  - Digital infrastructure – to enhance data storage, interoperability and security
  - Training and capacity building – to support effective data management.

(1) Including the existing restrictions on the collection and use of the data collected through compassionate use. (2) The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). General Principles on Plan, Design and Analysis of Pharmacoepidemiological Studies That Utilise Real-World Data for Safety Assessment of Medicines (M14). Published on 24 May 2024. See [link].

Two barriers limit effective price differentiation according to countries' ability to pay

Member States have varying abilities to pay for healthcare, largely determined by their wealth. At one end of the spectrum, Bulgaria (EUR 15 thousand) and Romania (EUR 17 thousand) have the lowest GDP per capita, while Luxembourg (EUR 119 thousand), Ireland (EUR 96 thousand), Denmark (EUR 63 thousand), and the Netherlands (EUR 60 thousand) rank among the wealthiest Member States, see Figure 5. Given these disparities in wealth, ensuring equitable access to medicines across the EU remains a challenge.

According to the OD Expert Group, one effective way to address differing ability to pay is for companies to price differentiate across markets, whereby they set higher prices in markets with greater ability to pay and lower prices in those with more limited resources. This approach, known as "**tiered pricing**," allows more equitable access while maintaining commercial sustainability. Many pharmaceutical companies already practice tiered pricing by setting different prices for the same treatment depending on a country's wealth, market conditions, or overall ability to pay.[1]

However, two barriers limit the effective price differentiation according to a country's ability to pay. These are parallel trade and external reference pricing.

Parallel trade

Price differences between Member States create arbitrage opportunities, where medicines sold at lower prices in one country are reimported and resold at higher prices elsewhere. This practice of parallel trade not only disrupts the supply of medicinal products in lower-income markets but also discourages companies from offering reduced prices in these markets. As a result, companies become hesitant to implement tiered pricing strategies that could otherwise improve equitable access across the EU.

External reference pricing

Today, 27 EEA countries use external reference pricing to benchmark medicine prices against other markets, limiting companies' flexibility to set prices based on a country's ability to pay.[2] While this practice helps payers negotiate lower prices, it has the unintended consequence of delaying access.

First, the use of ERP can contribute to access delays in countries with a lower ability or willingness to pay. This is the case when prices are cross-referenced across "not comparable" markets. Manufacturers postpone product launches in lower-income countries to avoid price erosion in higher-income markets.[3]

Second, in the presence of the ERP, the lack of publicly available price quotes also delays access. For example, until recently, Hungary required medicinal products to be marketed with reimbursement in three other EEA countries before they could be available domestically. ERP rules indicated that the price in Hungary could not be higher than the average of the three prices. This practice delayed access in cases where prices were not publicly available, e.g., if access conditions were regulated under PBMEAs.[4]

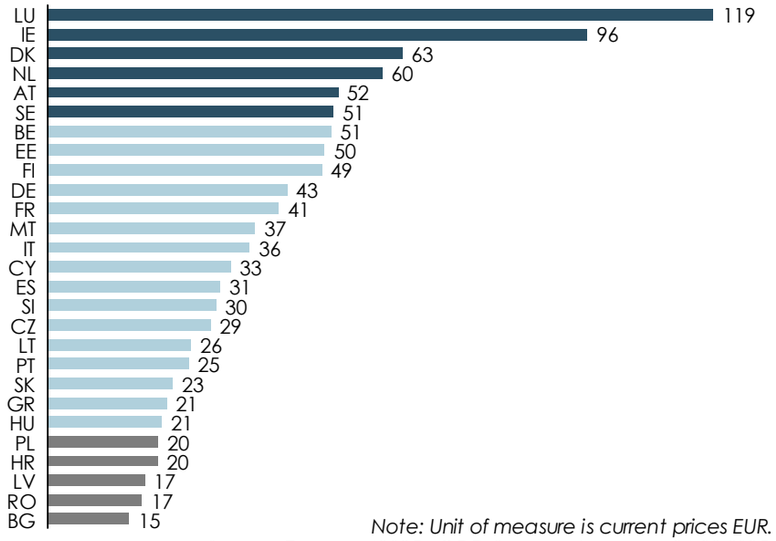
Third, developers may withdraw medicinal products from countries with a higher ability to pay if the publicly available price in such markets is unfavourable, as it will negatively impact pricing negotiations in other markets that use ERP. For example, an unfavourable net price negotiated in Germany, which could become publicly available, was one of the reasons Bluebird Bio withdrew a gene therapy from the EU, and Novartis withdrew the first-in-condition medicinal product from Germany.[5]

Recognising the challenges posed by ERP, some Member States have introduced policy measures to mitigate its impact. In 2023, Hungary revised its P&R laws and no longer requires a medicinal product to be reimbursed in at least three other EEA countries before approval in Hungary, facilitating earlier market access.[6] In 2024, Germany introduced an option for companies to keep negotiated prices confidential, preventing international price spillovers that could deter market entry.[7] Denmark has recently introduced a three-year pilot allowing confidential price discounts.[8]

While these national reforms are steps in the right direction, it is worth considering whether a more systematic EU-wide approach is needed to solve a country's ability to pay as a remaining hurdle for equitable access.

Figure 5. Member States differ in their wealth

GDP per capita 2023, EUR thousand



Note: Unit of measure is current prices EUR.
Source: Eurostat. (2025). GDP. See link. Accessed 24.03.2025.

(1) See for example Copenhagen Economics (2023). (2) Rand et al. (2021). Gill et al. (2019) or Maini, & Pammolli(2023). (3) For example, Cockburn et al. (2016) (4) "Hungary: Pricing and reimbursement reforms aiming to remove hurdles to late market access of innovative pharmaceuticals" published by Beker McKenzie on 29 May 2023. See [link]. (5) Under the current system, prices including the ex-manufacturer price, mandatory discounts and the price that companies negotiate with health insurers are publicly available and, as such, are used in ERP by other countries. (6) C.f. footnote (3). (7) Medizinforschungsgesetz or MFG. See [link]. (8) See Bech Brunn News published on 6 February 2025 [link].

Three EU-wide solutions for addressing differences in countries' ability to pay are on the table

Companies, patient organisations and policymakers put forward three solutions for further study that address the differences in countries' ability to pay. These are equity-based tiered pricing, joint procurement and an EU solidarity fund.

Equity-based tiered pricing

The equity-based tiered pricing (EBTP) solution is a framework that adjusts medicine prices based on a country's ability to pay.[1] This model builds on tiered pricing strategies already used by companies today. This framework can be strengthened if Member States commit to refraining from using external reference pricing and keeping prices confidential. The EBTP model could work as follows:

- *Defining tiers and pricing rules*. Countries should be categorised into tiers based on Gross National Income (GNI) adjusted for purchasing power parity (PPP). Prices in the lower tier must be lower than the lowest price in the upper tier, known as the "best price" rule. This principle is applied to the net price of a medicinal product at its first indication at launch to enhance access to innovation.
- *Member States should bilaterally negotiate prices with individual companies*. This allows pricing according to countries' ability to pay.
- *Confidentiality*. The prices of medicinal products in Europe are often referenced by third countries in their price control measures. Lowering official prices in some EU Member States will result in lower prices in third countries. Therefore, for the EBTP model to work effectively, the resulting price under EBTP must remain commercially confidential. Only in such a way can companies perfectly price-differentiate between Member States.
- *Commitment from the Member States to remove some forms of price controls,* such as external reference pricing, and ensure the non-extraterritoriality of national price controls.

Implementing this solution requires trust on both sides that Member States will not implement ERP and will keep actual prices confidential, and that developers will implement the differentiated pricing model.

Joint procurement

Joint procurement is a policy proposal put forward by Enrico Letta in April 2024.[2] Building on the success of jointly procuring COVID-19 vaccines during the pandemic, Letta suggests using a joint procurement mechanism for OMPs. According to Letta, such a solution would provide smaller countries with a structured framework to collaborate on procurement, promoting more equitable access across EU Member States. Letta also proposes the establishment of an innovative European Guarantee Fund specifically designed to help smaller countries overcome limited bargaining power. While this sounds like a promising idea, details are lacking on how the joint procurement mechanism and the fund could work in practice.

While the joint procurement mechanism worked for COVID-19 vaccines, its application to OMPs may be challenging. This is reflected in the experiences of two voluntary cross-country collaborations in HTA and pricing: FINOSE and BENELUXA. To date, only five rare disease treatments have undergone joint HTA and pricing negotiations, with negotiations lasting up to two years, see Table 1 on the next page. A common assessment of value, whether clinical or economic, should accompany joint procurement, but a solution has yet to be found. Furthermore, a WHO Report on voluntary cross-country collaborations to improve medicine access identified challenges for these initiatives, which included a lack of political commitment, differences between healthcare systems, and scarcity of resources to invest in the collaboration.[3] Letta's proposal offers little insight on how to address these challenges.

An EU solidarity fund

Financially supporting countries with lower ability to pay is yet another solution, brought forward in October 2022 by the European Economic and Social Committee (EESC). In its opinion, the EESC recommended reflecting on the possibility of creating a solidarity fund to ensure that the availability of funding is not a barrier to domestic and cross-border access.[4] Such a fund could draw inspiration, for example, from the 2002 EU Solidarity Fund for natural disasters and the lessons already learned from its implementation.

Similar to a joint procurement solution, a solidarity fund solution offers little insight into its design. The OD Expert Group points to the following challenges with its implementation:

- First, the *moral hazard*: The risk is that the fund could create a moral hazard, i.e. a situation where countries will be incentivised to overspend, knowing that the fund will cover the cost of expensive treatments.
- Second, *price transparency*: Member States contributing to the fund may demand greater transparency around OMP pricing. Greater price transparency will have implications for price negotiations in Europe and third countries.
- Third, *uncertainty in patient numbers*: The lack of robust epidemiological data on rare diseases means that patient numbers may fluctuate or be underestimated at the time of procurement. Clear volume commitments may be difficult to set, and Member States will need to agree on how adjustments should be funded.

Nonetheless, the OD Expert Group recognises the benefits of such a funding scheme in helping to reduce access disparities by supporting Member States with a lower ability to pay. It also sees funding as a tool to incentivise payers to adopt and companies to use early access solutions.

(1) See for example EFPIA (2022). (2) Enrico Letta's report on the future of the EU Single Market. See [link]. (3) WHO (2020). (4) EESC Opinion. Ensuring strong European solidarity for rare disease patients. SOC/(6) See p. 51 in Kamphuis et al. (2024).

2.2. Enable pricing according to the ability to pay

Table 1. Characteristics of the OMPs assessed in cross-country collaborations

	Treatment characteristics[1]			Marketing authorisation details[2]		Joint negotiations[3]		
Trade name	**Indication**	**Gene therapy product**	**Prevalence rate**	**EU market access date**	**EMA authorisation type**	**Initiative**	**Start and end dates - joint negotiations**	**Outcomes/Remarks**
Spinraza	Proximal spinal muscular atrophy	Yes	1-9/100,000	**May 2017**	• Accelerated assessment	Beneluxa	N/A - Jul. 2018	Joint pricing negotiations concluded
Zynteglo	Beta-thalassemia	Yes	1-9/1,000,000	**May 2019** Withdrawn	• Accelerated assessment • Conditional approval • ATMP	Beneluxa	N/A – Oct. 2021	Joint HTA not completed; the manufacturer withdrew the product
						FINOSE	N/A - Jun. 2020	HTA concluded
Libmeldy	Metachromatic leukodystrophy	Yes	1-9/1,000,000	**Dec. 2020**	• Additional monitoring • ATMP	Beneluxa	Feb. 2022 - Jan. 2024	Joint pricing negotiations failed
						FINOSE	N/A - Feb. 2023	HTA concluded
Voxzogo	Achondroplasia	No	Incidence rate of 1/25,000 live births worldwide	**Aug. 2021**	• Additional monitoring	FINOSE	N/A - Sept. 2023	HTA concluded
Hemgenix	Haemophilia B	Yes	1-9/100,000	**Feb. 2023**	• Conditional approval • Additional monitoring • ATMP	Beneluxa	Oct. 2023 – Ongoing	Joint HTA process started

Source: (1) Orphanet data. (2) EMA website. See [link]; (3) BENELUXA Website. See [link]; FINOSE website, See [link].

Removal of structural barriers and adjustments in accounting rules may further support ability to pay

Enabling pricing according to ability to pay is not only about acting on big policy proposals. Removing structural barriers to the implementation of innovative contracting schemes, such as PBMEAs, is equally important.

Linking payments to outcomes enables payments to be made over time, aligned with the therapy's performance

PBMEAs are recognised by the OD Expert Group as a best practice to speed up access to treatments for therapies that provide long-term or potentially curative benefits, see Section 2.1 of this report.

Such agreements also increase the ability to pay because they allow payers to spread costs and risks over time, often across several years, based on the observed outcomes in individual patients. To illustrate how they work in practice, consider a one-off disease-modifying therapy, a potentially curative advanced medicinal product (ATMP). Such a therapy costs between approximately EUR 300,000 and EUR 2.5 million.[1] Under PBMEAs, the payer and manufacturer agree that payments can be made over several years and are conditional upon the patient achieving agreed clinical outcomes. Should the therapy prove ineffective at any point during the payment schedule, the payer is not required to cover the remaining cost, which remains the responsibility of the manufacturer. This approach not only improves affordability for payers but also facilitates a more balanced distribution of financial risk between the payer and the developer.

National interpretation of the EU accounting rules may not allow spreading payments over time

For the payment to be spread over time, consistent accounting methods must be applied to allocate the cost of such therapies to the financial years in which the payments are contractually due. However, existing national accounting rules and systems of financial control may limit the feasibility of implementing such annual payment schemes.

Under the European System of Accounts, ESA 2010, reimbursed medicinal products are considered a *social transfer in kind* (D.63).[2] This means the total cost of the therapy reimbursed must be budgeted in the balance sheet in the year when it is incurred (accrual), regardless of when the actual payments are made. As a result, although payments may be scheduled across future years, the entire expenditure must be budgeted upfront. This mismatch between accounting recognition and cash flow can lead to significant budgetary control challenges, undermining the practical application of annuity-based payment schemes.

Italy is an example of a country that considers the reimbursement of medicinal products, including ATMPs, as *a social transfer in kind*, a practice that does not allow the effective implementation of annuity payment schemes and therefore creates a barrier for the implementation of PBMEAs. Such a structural barrier could be removed if these expenditures were considered *an investment* rather than *a social transfer in kind*, allowing hospitals to carry related expenditures into a new fiscal year,[3] better aligning budget treatment with the structure of PBMEAs.

Achieving this requires further clarification of EU accounting standards and corresponding adjustments to national financial frameworks to support annuity payment schemes.

(1) See p. 27 in Alleva, et al. (2023). (2) See p. 113 par. 4.110 in the European System of Accounts– ESA (2010). (3) Alleva, et al. (2023).

Call to Action

Enable pricing according to ability to pay

Member States' differing ability to pay remains a major hurdle for equitable access to OMP across the EU. While proposals formore systematic EU-wide solutions are on the table, their impacts and feasibility have not been studied or tested. Moreover, simple administrative hurdles may further hamper the ability to pay for highly innovative treatments. The OD Expert Group, therefore, calls on the European Commission and Member States to take the following actions:

8. Implement equity-based tiered pricing through a pilot programme for selected disease treatments

- Equity-based tiered pricing is the most mature proposal that allows its implementation. Companies are ready to apply tiered pricing strategies. Currently, prices are negotiated at the national level, and some countries are introducing confidentiality around prices and removing external reference pricing price controls.
- The European Commission should implement equity-based pricing as a pilot programne for a set of selected rare-disease treatments. The pilot should be co-developed with broad stakeholder representation.
- This pragmatic approach will foster the implementation of best pricing practices, test the solution in a real-world setting, assess efficacy, and identify potential challenges for full-scale implementation.

9. Assess the impact of joint procurement on equitable access to OMPs and competitiveness

- The European Commission should assess the impact of joint procurement on early and equitable access to OMPs and conduct a competitiveness check through a dedicated initiative.

10. Explore the use and feasibility of an EU solidarity fund

- The European Commission should explore the use and feasibility of an EU solidarity fund or similar financial mechanism as a strategic tool to drive earlier and more equitable access to OMPs.
- To move this forward, the Commission should establish a dedicated platform for stakeholder collaboration to address practical and policy challenges around the fund's design and implementation.

11. Clarify EU accounting rules to promote access

- The European Commission should provide clear and harmonised guidance on the classification of therapies with long-term, disease-modifying and potentially curative effects, such as ATMPs, within the European System of Accounts. This would support consistent account treatments across Member States.
- The European Commission should place this topic on the agenda of meetings with National Competent Authorities on Pricing and Reimbursement (NCAPR) and public healthcare payers, to identify inconsistencies and gaps. It should further use this platform to promote alignment and practical implementation at the national level.

(1) The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). General Principles on Plan, Design and Analysis of Pharmacoepidemiological Studies That Utilise Real-World Data for Safety Assessment of Medicines (M14). Published on 24 May 2024. See [link].

3
ENABLE EFFECTIVE ACCESS TO CROSS-BORDER HEALTHCARE

The existing cross-border healthcare framework creates administrative and payment barriers restricting patient access

Patient access, the actual administration of medicinal products to patients, is not solved when P&R agreements are in place, but only when the OMP reaches people living with a rare disease.

People living with a rare disease may **experience delays in accessing treatment due to limited expertise and a lack of infrastructure** in their home country. In many Member States, specialised knowledge in complex rare diseases is often lacking simply because the patient population is too small to sustain specialised knowledge and skills. Furthermore, special technology or skills may be required to administer treatment, and these may not be available in the home country. As a result, people living with a rare disease can be forced to seek treatment abroad or in designated expert centres, facing logistical and financial challenges.

This, for example, is the case for *Stimvelis*[1], characterised by an extremely short shelf life; *Upstaza*,[2] which is infused into the brain using a specific technique, *and Libmeldy,*[3] which must be administered in a qualified treatment centre with experience in haematopoietic stem cell transplantation. All three treatments are designed for ultra-rare, life-threatening, or severely debilitating childhood diseases.

The EU has a **regulatory framework designed to facilitate cross-border healthcare access**. This framework, however, needs to be further improved to eliminate administrative hurdles, address financial budgetary and payment barriers, and improve the quality of decisions taken by Member States regarding access to cross-border healthcare with access to OMP treatments.

Currently, in the EU, access to cross-border healthcare is facilitated with two funding routes. The Directive on Patient Rights in Cross-Border Healthcare[4] allows patients to travel to another EU Member State for treatment and have the cost *reimbursed from* their national health insurance scheme. The funding scheme requires that patients pay upfront and seek reimbursement later, creating financial barriers. Furthermore, the Regulation on the Coordination of Social Security Systems[5] facilitates *planned* cross-border healthcare by connecting social security systems across Member States. Planned access requires *prior authorisation* to ensure coordinated payments between social security systems. The Regulation applies only when the treatment cannot be provided in the home country within a medically justifiable time.[6]

While the current framework facilitates cross-border access to OMPs, it imposes an **administrative burden** on people living with a rare disease and **creates budgetary and payment barriers** that make access to cross-border healthcare challenging.[7]

The *authorisation process* for access to cross-border healthcare presents two key challenges for patients:

- *The patient must initiate the authorisation request*. Unlike regular national procedures, where treating specialists handle authorisation requests, patients themselves must submit applications for access to cross-border healthcare.[8] This creates an unnecessary administrative burden, especially for individuals managing complex health conditions.
- *Patients may be asked to submit additional documentation.* There is room for discretion when handling authorisation requests under the Directive, and additional documentation may be requested. Such requests may slow or even derail access to cross-border healthcare.

Beyond these administrative hurdles, further budgetary and payment barriers exist. These include:

- *Cost coverage*. Currently, the *prior authorisation* covers treatment costs only. Travelling and accommodation costs are not covered, which can create a significant barrier to access, especially for longer treatment periods where the presence of a caregiver is necessary.
- *Price discrepancies between Member States*. The price that needs to be paid is the *list price* of the host country, which may be higher than the negotiated price in the home country. For high-priced medicinal products, this gap can be substantial.
- *Contracting limitations.* The current framework places significant limitations on the implementation of performance-based agreements. The home country social security system remains responsible for covering treatment costs, but the host country (where treatment takes place) provides care under the conditions applied to its citizens. Home country payers, therefore, struggle to implement managed entry agreements that require monitoring and follow-up.

Because of these barriers, people living with a rare disease who have unmet needs can find themselves in difficult situations where the OMP treatment they need has been approved in the EU and has received P&R status in their home country, but they must wait until it is possible to administer it domestically instead of receiving it abroad immediately.

If cross-border access OMP is to be effective, the current framework requires reform in two key areas: improving prior authorisation processes and financial rules. Without these changes, the framework meant to facilitate access will continue to function as a barrier for those who need it most.

(1) A treatment of a severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID). (2) Approved for severe aromatic L-amino acid decarboxylase (AADC) deficiency. (3) Approved to treat metachromatic leukodystrophy (MLD). (4) Directive 2011/24/EU on the application of patients' rights in cross-border healthcare. See [link]. (5) Regulation (EC) No 883/2004 on the coordination of social security systems. See [link]. (6) HICT (2022). (7) For a comprehensive overview, see Table 1 in HICT (2022) Background Material. (8) This is, for example, the case in Belgium today.

ERNs have specialised expertise but are not fully integrated into the framework guiding access to cross-border healthcare

ERNs have their roots in cross-border directives, but their role in access to cross-border healthcare is limited

Established to improve access to specialised healthcare for patients with rare or complex diseases, **ERNs** bring together expertise from across Europe.[1] Their purpose is to facilitate knowledge sharing, coordinate research, and enhance diagnosis and treatment options by connecting highly specialised centres. By fostering collaboration among healthcare providers, ERNs aim to reduce disparities in care and ensure that patients benefit from the best available medical expertise, regardless of their location.

ERNs ensure that people living with a rare disease receive specialised care as close to home as possible. By sharing expertise across borders, they enable local centres to diagnose and treat patients, minimising the need for travel. Only in the most complex cases, where treatment is not feasible locally, do ERNs guide patients to specialised centres best equipped to provide the necessary care.[2]

Despite their expertise, ERNs currently play a limited role in access to cross-border healthcare, missing opportunities to improve the decision-making process for people living with a rare disease seeking treatment abroad.

Giving ERNs an advisory role will improve the quality of decisions taken across the Member States

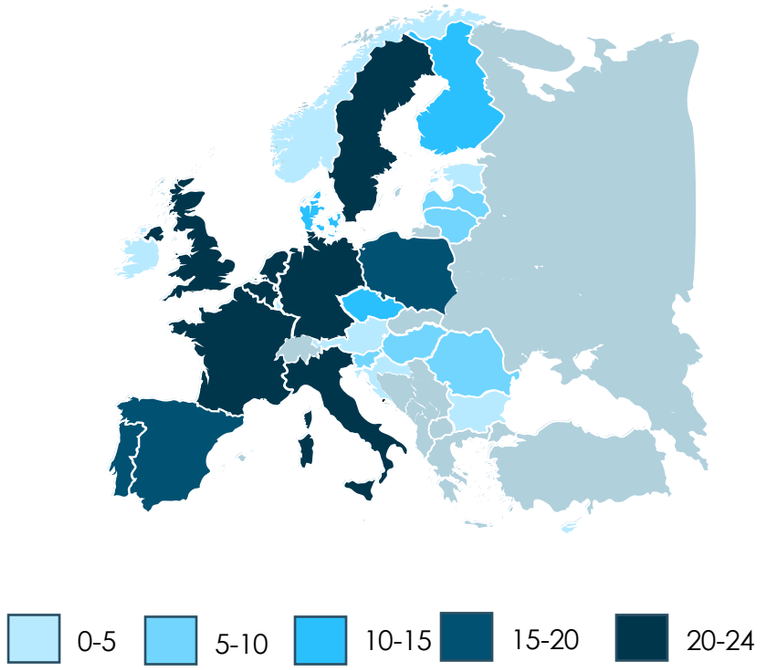
ERNs should be given a legal mandate to serve an advisory role in decision-making on face-to-face cross-border healthcare requests, ensuring their expertise is systematically integrated into the process. With their expert input, national authorities could more confidently grant approvals for treatment abroad. Embedding ERN expertise into the referral and authorisation process would ensure that medical decisions guide whether a patient can travel for care.

This can be achieved by embedding ERNs and/or their centres through a structured coordination mechanism into the National Contact Points (NCPs), which play a key role in providing information and guidance to patients about their rights, the authorisation process, and the required documentation. As part of this approach, NCPs would routinely consult ERNs or their centres during the review of requests for rare disease treatments and care, improving the quality and consistency of cross-border healthcare decisions.

Furthermore, a third-country ERN centre could provide advisory support domestically if no specific centre exists within the country. Given ERNs' expertise in complex, rare diseases, leveraging their knowledge, regardless of geographic location, could help ensure better access to appropriate care. However, this would require a formal mechanism for recognising third-country ERN input within the national healthcare framework.

Since only a few Member States, such as France, Italy, and Germany, have centres covering all therapeutic areas of rare diseases, enabling third-country ERN centres to provide advisory support would benefit all countries by filling gaps in expertise, see Figure 6.

Figure 6. Number of ERNs by treatment area per country



Notes: The figure shows the number of ERNs by treatment area per country. Please note that one ERN treatment network may have more than one member in each country. Source: Copenhagen Economics based on European Commission overview of ERN networks. See [link].

(1) ERNs have their roots in Article of the 12 Directive 2011/24/EU on the application of patients' rights in cross-border healthcare. See [link]. (2) See the European Commission website on Public Health [link].

Facilitating effective cross-border access to disease-modifying and potentially curative OMPs may require new solutions

Best practices can be found outside the EU regulatory framework

Other solutions outside the cross-border framework are emerging to facilitate efficient cross-border access to specialised care and treatments.

Bilateral agreements between local payers and foreign treatment centres

In parallel to the Directive and Regulation, examples of national **bilateral agreements** enable access to cross-border healthcare. One example is a bilateral agreement between Germany and Belgium (Ostbelgien Regelung) that facilitates access to specialised care. This bilateral agreement builds on the funding route available under regulations by simplifying the procedure for cross-border healthcare under certain conditions, thus removing an administrative hurdle for cross-border treatments.[1]

Another example concerns the special reimbursement for hadron therapy in Belgium that utilises a German treatment centre to allow Belgian patients access to this innovative treatment.[2] Here, the agreement is between the Belgian payer of the home country (Belgium) and a treatment centre abroad. This route is covered in more detail in Box 3.

A recent paper suggested a "backpack" solution

The **backpack solution** involves the patient metaphorically "carrying" the necessary medicinal product from their home country to the foreign treatment centre. Essentially, the treatment centre in the home country orders the medicinal product, which is then delivered to a treatment centre abroad equipped to administer it.[3] This is a proposal for possible cross-border access to ATMP or an invasive therapy that could address problems with the current cross-border framework.

This arrangement bypasses traditional cross-border pharmaceutical logistics, as the medication is ordered and paid for under the home country's pricing and reimbursement agreements but delivered and administered abroad.

The pharmaceutical company ships the treatment directly from the home country to the foreign treatment centre. This is arranged and managed by the pharmaceutical company and the foreign treatment centre, ensuring that the product meets all necessary conditions for safe and effective use upon arrival.

Financial arrangements for the treatment, including reimbursement and any managed entry agreements (compensations), are handled as if the treatment were administered domestically. This means the home country's healthcare system processes payments and reimbursements according to its established tariffs and agreements, without involving the foreign country's payment systems.

The benefits of a backpack solution are threefold. First, it simplifies the reimbursement process by applying the home country's established drug pricing and reimbursement mechanisms. Second, it avoids the complexities of international drug pricing disparities and VAT differences. Finally, it ensures that manufacturers receive payments under the home country's pricing agreements, facilitating straightforward executions of managed entry agreements.

The backpack solution also has limitations, as it primarily addresses the logistical and financial aspects of drug provision and does not inherently resolve other costs related to treatment abroad, such as travel, accommodation, or non-drug medical expenses. Furthermore, legal challenges might arise, particularly concerning the prescription and administration of treatments that are not directly procured by the treating hospital abroad.

Box 3. Hadron therapy: A case study of bilateral treatment agreements

Hadron therapy, specifically proton beam therapy, is an innovative cancer treatment method known for its precision. It minimises radiation exposure to healthy tissue surrounding tumours, thereby reducing potential side effects. Although not an orphan medicinal treatment, the access pathway for proton beam therapy is a useful case study of bilateral agreements enabling access to innovative treatments.

Before 2020, proton beam therapy was not available in Belgium and was not covered by the compulsory health insurance. However, it was available in five specialised centres located in France and Germany.

To facilitate access to this therapy for Belgian patients, a royal decree was issued enabling the Belgian health insurance scheme to finance treatment abroad. Under this agreement, the costs of treatment, travel, and accommodation are covered for patients referred by a certified Belgian radiotherapy centre. In addition, the referring radiotherapy centre receives a fixed financial contribution to cover the administrative work related to the referral. Authorisations are granted by an agreement.

This royal decree remains in effect today, as a small number of patients still need to be referred to other centres for treatment options that are not available in Belgium.

Source: HICT (2022)

(1) The conditions that mainly apply are related to locations and type of treatment. See HICT (2022). (2) Werbrouck et al. (2023). (3) HICT (2022).

Call to Action

Enable effective access to cross-border healthcare

The current cross-border healthcare framework imposes administrative and financial barriers, restricting access to specialised care for people living with a rare disease where such care and treatments are available in a Member State other than their country of residence. Despite the specialised expertise of ERNs, their role remains limited in facilitating patient access. Instead, reliance on bilateral agreements outside the EU framework has emerged as a best practice, highlighting gaps in the current system. To ensure effective access to cross-border healthcare for people living with a rare disease, the OD Expert Group calls on the European Commission and Member States to take the following actions:

12. Improve the authorisation process and address budgetary and payment barriers in cross-border healthcare

- The European Commission should analyse how rules on authorisation are applied across Member States, ensure the process aligns with the legislation's intent and respects patients' rights, and is fair, avoiding excessive demands for information.
- Member States should fully implement the provisions of Directive 2011/24/EU, Article 9.5, by ensuring reimbursement for people living with a rare disease seeking access to cross-border healthcare. This step is critical in removing budgetary barriers.
- The European Commission should use the existing platforms to:
  - encourage dialogue on the feasibility of the "backpack solution";
  - seek solutions to effective "patient follow-up" in the context of access to cross-border healthcare.

13. Grant ERNs a legal mandate to perform an advisory role in access to cross-border healthcare

- Policymakers should grant ERNs a legal mandate to serve as advisory experts in access to cross-border healthcare.
- ERN expertise, for example, could be integrated into NCPs and national healthcare systems more broadly to ensure that people living with a rare disease receive the best possible care across borders.
- This advisory role of ERN should be prioritised and formally discussed within the framework of the Joint Action JARDIN under the EU for Health Programme, which seeks to integrate ERN activities into national healthcare systems.[1]

14. Monitor and mitigate excessive restrictions on free movement of persons

- Member States should make it easier for patients to use their rights to access cross-border healthcare.
- Excessive restrictions on the free movement of people (patients) should be avoided. The European Commission should issue a Communication on what it considers necessary to avoid excessive restrictions.

15. Raise awareness about access to cross-border healthcare among healthcare professionals

- The European Commission and Member States should raise awareness among healthcare professionals about patients' rights to cross-border healthcare, to ensure that people living with rare diseases can access timely, specialised treatment not available in their home country.

(1) European Commission, News Announcement, Commission launches joint action with €18 million funding to improve the diagnosis, treatment and care of patients with rare diseases, 8 March 2024 [link].

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