

# REWIRING RESEARCH FUNDING TO DELIVER IMPACT IN RARE DISEASE WHITE SPOTS

The Rare Disease Moonshot contribution to the EURORDIS'  
Blueprint for an EU Action Plan on Rare Diseases  
– May 2026

# EXECUTIVE SUMMARY

In European rare disease research, the main challenge often lies not in discovery itself, but in the progression of promising scientific outputs into assets that are sufficiently robust, usable and mature to support further development, regulatory engagement and, ultimately, impacting people' lives. This challenge is especially acute in rare disease white spots, where scientific knowledge, infrastructure, data resources and commercial incentives are weak from the outset. The problem is therefore not only the level of funding, but how funding is structured, deployed and connected to downstream use.

The white paper shows that this is a systemic issue. Across the ecosystem, responsibility is distributed but progression is not owned. Funders support discrete stages, researchers deliver within project boundaries, regulators and HTA bodies intervene at specific moments, and industry engages selectively once projects reach a certain maturity. Between these stages, however, there is no clear organising function to preserve momentum, support maturation, or ensure that outputs become ready for the next user in the chain. As a result, many projects stall for reasons that are structural rather than scientific. Current incentive and evaluation systems reinforce this pattern. Researchers respond to what is rewarded: publications, novelty, feasibility, grant success and institutional visibility. Activities that matter for progression, such as validation, reproducibility, standardisation, data curation and early alignment with downstream expectations, remain less valued. Evaluation frameworks also tend to favour fields that already have the cohorts, infrastructure and prior data needed to compete, leaving white spots at a structural disadvantage.

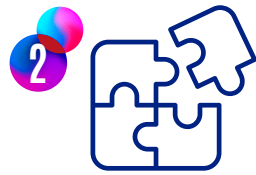
The paper also identifies the "messy middle" as the main bottleneck. Validation, de-risking, reproducibility, development planning, and early regulatory and HTA alignment require dedicated support, but are too often treated as implicit extensions of discovery. In parallel, shared infrastructures such as registries, cohorts and curated data assets remain fragmented and fragile. Progress therefore depends too heavily on ad hoc arrangements, informal networks and individual capacity. The core conclusion is clear: Europe needs not only more investment in rare disease research, but a rewiring of research funding so that progression itself becomes an object of design, support and governance.

## Three key recommendations

The combined impact of the three recommendations below on research would be direct as they would support research produce outputs that are not only scientifically strong, but also better prepared for the next step. More projects would be carried through the transition points where momentum is usually lost. More results would be validated, better documented, more reusable, and earlier aligned with regulatory, HTA, clinical or development expectations. And in white spots especially, they would reduce the risk that promising work stops simply because the system is not set up to carry it forward.



### GOVERNANCE



### PRACTICAL GAP IN THE PATHWAY



### BEHAVIOUR AND CAPABILITY

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**1** The first recommendation addresses **governance**. Giving public funders a clearer stewardship role means that someone is actively looking across the pathway, identifying which projects or assets are worth advancing, where they are getting stuck, and what kind of support is needed next. Without that function, promising work can still be lost even if funding exists somewhere in the system. Stewardship creates direction, continuity and accountability for progression.

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**2** The second recommendation addresses **the practical gap in the pathway**. Even when a project has strong potential, it often reaches a stage where discovery funding is no longer enough, but development support is still out of reach. That is where validation, reproducibility, de-risking, and early regulatory or HTA alignment become critical. Shared infrastructures, cohorts, datasets that are well maintained can help with the transition of the scientific results and excellence into innovation. Dedicated progression funding gives researchers a way to do that work deliberately, rather than hoping it can be squeezed into existing grants or picked up later by another actor. In other words, stewardship helps identify what should move forward; progression funding makes it possible to do so.

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**3** The third recommendation addresses **behaviour and capability**. Even with better oversight and better funding instruments, the system will still underperform if researchers are mainly rewarded for publications and novelty, while the work needed to make outputs usable downstream remains undervalued. Realigning incentives (inc. careers), support structures and infrastructure makes it more likely that projects are designed from the outset with future use in mind. It also gives researchers access to the tools, expertise and training they need to produce outputs that others can actually adopt, build on or translate.

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# METHODOLOGY

The objective was not to produce a representative sample, but to capture informed, experience-based perspectives from actors directly involved in shaping or navigating the system. A series of semi-structured interviews was conducted with stakeholders spanning the full research and innovation pathway, including public and private funders, academic and clinical researchers, industry representatives, regulators and HTA experts, as well as patient representatives. Interviews explored three core dimensions: how funding mechanisms influence behaviour and collaboration; where and why promising projects lose momentum; and what structural changes could better support progression, particularly in rare disease white spots.

The findings were further interpreted through the lens of the Rare Disease Moonshot's work on public-private partnerships and research-to-impact pathways. This allowed the analysis to move beyond diagnosis towards identifying actionable levers for change.

## Interviewees (stakeholders and organisations)

PUBLIC FUNDER	ZonMw	Research	Critical Path Institute
	ZonMw	Patient representative	CTF Europe
PRIVATE FUNDER	Fondazione Telethon	Patient representative	EURORDIS-Rare Disease Europe
RESEARCH	ERDERA	Patient representative	EURORDIS-Rare Disease Europe
	Leuven Institute for RDs	Pharmaceutical industry	EFPIA
	EATRIS	Pharmaceutical industry	Sanofi
	BBMRI	Pharmaceutical industry	Industry expert
	ECRIN	HTA	HTA expert

# DIAGNOSIS AND RECOMMENDATIONS

## WITHOUT ACTIVE STEWARDSHIP FROM PUBLIC FUNDERS, PROGRESSION ACROSS THE PATHWAY WILL CONTINUE TO STALL

At the centre of the European rare disease research ecosystem lies a structural ambiguity: no actor is explicitly responsible for ensuring that promising scientific outputs progress across the full pathway. Public funders, researchers, infrastructures, regulators, patient advocacy groups, and industry all contribute within clearly defined roles; yet these roles are organised around discrete functions, not around continuity. Responsibility is distributed, but progression is not owned, as there is no stewardship, creating a sequence of partial mandates. Funders support defined stages through time-limited instruments. Researchers deliver projects aligned with those scopes. Regulators and HTA bodies intervene at specific checkpoints. Industry engages selectively once assets reach a certain level of maturity. Between these stages, however, there is no organising function tasked with maintaining trajectory, preserving momentum, or ensuring that outputs are sufficiently matured to be taken forward reflecting a structural division of roles between academia and industry, where neither side is currently equipped or incentivized to fully bridge the transition. Expecting academic researchers to cover the full spectrum of translational requirements is neither realistic nor efficient.

As projects advance, the nature of the challenge shifts from scientific exploration to validation, standardisation, and development planning. These later stages require different capabilities, longer timelines, and more structured alignment with downstream requirements. Yet this is precisely where ownership becomes diffuse. Teams are reconfigured, contractual arrangements lapse, and accumulated knowledge is not systematically retained or developed further meaning that outputs may be scientifically robust but insufficiently prepared for use.

Public funders have a central, though often under-recognised, role in shaping this dynamic. Through call design, eligibility criteria, evaluation frameworks, and monitoring systems, they do more than allocate resources as they define the operating logic of the system. They influence what is valued, what is feasible, and what is sustained. Yet this shaping function remains only partially exercised in favour of downstream progression. Translational ambition is frequently encouraged in principle but rarely specified in operational terms. Calls refer to “impact”, but do not consistently define what constitutes development readiness, usability, or progression to the next stage. Moreover, evaluation and monitoring frameworks reinforce this limitation. Selection processes continue to prioritise conventional markers of scientific excellence, while progression-related dimensions (validation, data robustness, alignment with regulatory, HTA or patients’ expectations) are unevenly assessed. Monitoring focuses on outputs such as publications or deliverables but does not systematically track whether results are becoming usable, transferable, or ready for further development. As a result, continuation decisions are weakly linked to maturation, and promising assets are not consistently identified or supported beyond the initial funding cycle.

This does not reflect a lack of intent but public funders operate under real constraints: the need to ensure fairness in competitive allocation, accountability for public spending, political oversight, and limited flexibility within programme cycles. Designing instruments that balance openness, excellence, and strategic direction is inherently complex. However, the current configuration tends to reproduce fragmentation rather than counteract it.

All together, these dynamics point to a systemic gap: the absence of an organising function that treats progression itself as an object of governance. Without a more explicit form of stewardship and particularly from those actors that already structure the system promising work will continue to stall for reasons that are structural rather than scientific. Public funders are uniquely positioned to address this gap as strengthening progression across the pathway does not require creating entirely new actors, but rather expanding and strengthening the capacities and capabilities of public funders.

## Recommendations

- > **Funders should move beyond funding isolated projects and adopt a more explicit stewardship role at portfolio level.** This implies tracking assets over time, identifying those with progression potential, and maintaining visibility across stages rather than within single grants.
- > **Deployment of capacity building program targeting funders** to enhance this stakeholder to take up this stewardship role.
- > **Implement multidisciplinary advisory committees to support researchers and funders during the project.**
- > **Calls for proposals should encode clearer development logic** rather than relying on broad notions of impact but rather define more concretely what progression entails aligning de facto expectations across researchers, evaluators, and subsequent users of the outputs.
- > **Evaluation frameworks should be broadened** to reflect this shift with panels incorporating a wider range of expertise, including patient representatives, regulatory, HTA, clinical development, and data specialists, so that progression potential is assessed alongside scientific quality. This does/should not replace excellence criteria but complements them with a more forward-looking perspective.
- > **Monitoring systems should evolve from tracking activity to tracking maturation** by the assessment of whether results are becoming usable and use these signals to inform continuation or follow-on support.

# INCENTIVES AND EVALUATION SYSTEMS MUST BE REALIGNED TO SUPPORT PROGRESSION AND UNLOCK RARE DISEASE WHITE SPOTS

Researcher behaviour within the rare disease ecosystem is largely a rational response to the incentive structures that shape academic life. Researchers optimise for what is consistently recognised and rewarded: publications, novelty, grant success, institutional visibility, and career progression. Although the discourse around impact has become more prominent, it is rarely reflected in concrete career consequences (such as more senior position and increased salaries). Even where translational support structures exist such as technology transfer offices, expert networks, or regulatory advisory mechanisms their uptake remains limited if engagement with these resources does not translate into tangible career benefits. Without a clear link between such activities and professional advancement, researchers have little incentive to invest time in engaging with regulatory, IP, or downstream development processes. Engagement with regulatory, IP, or translational infrastructures requires significant time and effort, yet it seldom translates into tangible recognition, advancement, or improved working conditions.

As a result, activities that are less visible or less rewarded such as validation, reproducibility, standardisation, data curation, or alignment with downstream needs tend to be deprioritised, regardless of their importance for research project progression. This is reinforced by evaluation systems that assess project proposals against criteria that are robust and defensible, but also strongly anchored in research maturity: preliminary data, methodological readiness, established teams, existing infrastructures, and credible feasibility signals. While these criteria are individually justified, they collectively favour areas that are already well-developed and organised. They reward readiness more than potential, and continuity more than initiation.

Moreover, many public funders do not have (a) specific programme(s) for rare disease research. The researchers have to apply to different programmes of one funder or several funders; each programme is managed by other people with different backgrounds. The program managers do not know about the needs for rare diseases, about possibilities in other programmes that may help the researchers carrying on a rare disease research project to the next translational phase.

Rare disease white spots lack the very elements that evaluation systems expect to see: cohorts, registries, prior data, or established networks, creating a structural disadvantage. Their weakness is not necessarily scientific; it is infrastructural and therefore are often non-competitive before selection even begins. Even when calls explicitly refer to unmet need or innovation, funding decisions tend to concentrate on areas where feasibility is easier to demonstrate and risk is easier to defend. Over time, this produces a self-reinforcing dynamic. Funding flows towards diseases and domains that already benefit from prior investment, while white spots remain excluded from the cycle that would allow them to build the assets required to become competitive amplifying the disparities.

The consequence is not simply uneven distribution of resources, but a structural misalignment between policy ambition and operational reality. While the system calls for innovation, unmet need, and impact, it continues to reward scientific productivity and feasibility more consistently than translational progression or first-in-field exploration.

## Recommendations

- > **Evaluation and funding criteria should be rebalanced to recognise progression-oriented contributions alongside scientific excellence** to give greater weight to validation plans, data robustness, reusability, and alignment with downstream development pathways.
- > **Ensure that translational support structures are coupled with incentive reforms.** The availability of regulatory, IP, or development support is insufficient if engagement with these resources does not contribute to career progression, funding success, or institutional recognition.
- > **Dedicated entry routes should be created for rare disease white spots.**
- > **Scoring frameworks should be adapted for first-in-field and exploratory work.**
- > **Career advancement and recognition frameworks should better value contributions to translational outputs and engagement with downstream stakeholders.**

# THE SYSTEM FAILS IN THE TRANSITION TO DEVELOPMENT READINESS AND MUST BE REDESIGNED TO SUPPORT PROGRESSION

In the transition from scientific output to development-ready assets, often described as the “messy middle”, is where momentum is most frequently lost, and where structural weaknesses become most visible. In practice, this phase involves operational bottlenecks: validation, reproducibility, standardisation, and early regulatory positioning.

This transition is not a single step but a sequence of demanding activities: validation, reproducibility, standardisation, de-risking, development planning, and early regulatory and HTA alignment. These tasks are slower, less visible, and more resource-intensive than discovery and require operational discipline, specialised expertise, and sustained coordination across actors. Yet they are not consistently supported as a distinct phase within the funding architecture. Instead, they are treated as implicit extensions of discovery or as precursors to development, without dedicated instruments or clear ownership. As a result, projects enter a zone where expectations increase but support fragments and work that is scientifically robust begins to encounter new requirements (regulatory positioning, endpoint definition, comparators, patient relevance, data quality standards) that were not anticipated or embedded at earlier stages. Addressing these gaps often requires redesign, additional studies, or access to capabilities that are not readily available. In many cases, projects stall not because the science is insufficient, but because the conditions for progression have not been created. Unfortunately, this is reinforced by how research is designed from the outset as publicly funded projects are frequently structured around internal scientific logic, with limited anticipation of downstream use. Questions of who might adopt the outputs, under what conditions, and with what evidentiary expectations are not always addressed early enough. As a result, outputs that are scientifically valid may not be immediately usable by the next actor in the chain whether regulators, HTA bodies, developers, or investors.

Regulatory and HTA considerations, although decisive for future value, are often introduced late in the process, once key design choices have already been fixed. At that stage, adapting endpoints, comparators, or data structures becomes costly and sometimes infeasible. In rare diseases, where populations are small and opportunities to generate data are limited, early misspecification can have lasting consequences. The system thus treats downstream requirements as constraints to be addressed later, rather than as elements that could guide more efficient design from the beginning.

The funding architecture itself contributes to this fragmentation. Research is still predominantly organised as a sequence of stand-alone projects with fixed timelines and scopes each stage requiring a new application, often under different criteria and with reconfigured consortia. This stop-start dynamic interrupts continuity, delays progression, and weakens the cumulative value of prior investment. Teams shift focus from advancing work to securing the next grant; datasets are underutilised; partnerships dissolve and must be rebuilt and therefore promising assets are repeatedly reset rather than progressively matured.

These challenges are amplified in rare disease white spots. In these areas, the absence of prior knowledge, infrastructures, and industrial interest makes the transition to development readiness inherently more fragile. In some cases, this goes further: there is no realistic expectation that industry will engage at later stages, given the very small patient populations and limited commercial incentives. The implicit assumption that publicly funded research will eventually be taken forward by private actors therefore does not hold. As a result, projects are not only exposed to the general weaknesses of the 'messy middle' but also to a structural gap in responsibility for downstream development. This suggests that, for a subset of rare disease white spots, public funding strategies may need to extend beyond early research and explicitly support the full progression pathway, rather than relying on eventual handover. Without funding models and governance frameworks that explicitly account for this, many promising efforts are likely to stall before reaching clinical application.

## Recommendations

- > **Create dedicated instruments for the transition to development readiness, with specific provisions for rare disease white spots where no private handover can be assumed.** In such cases, funding should support progression beyond early validation, including later-stage translational and development activities.
- > **Validation, reproducibility, de-risking, and early regulatory alignment should no longer sit as implicit extensions of discovery.** They require their own funding logic, with resources calibrated to the operational and evidentiary demands of this phase.
- > **Funding instruments should support continuity alongside initiation** with milestone-based frameworks evaluated against meaningful indicators of maturation, not administrative checkpoints. Follow-on grants, staged funding, and progression-based support mechanisms can help ensure that work is not only started, but meaningfully advanced. The objective is not to reduce competition or accountability, but to ensure that effort is not repeatedly lost at transition points.
- > **Proposals should not only describe the science, but also outline who might use the outputs, under what conditions, and what would make them usable.**
- > **Bring regulatory and HTA perspectives into the picture sooner through light-touch, accessible advisory mechanisms** that inform study design before key parameters are fixed, reducing the need for costly redesign later.

# STRENGTHENING CAPABILITY AND INFRASTRUCTURE IS ESSENTIAL TO ENABLE PROGRESSION IN RARE DISEASE RESEARCH

Public researchers are increasingly expected to operate well beyond the boundaries of traditional academic roles. They are asked to anticipate regulatory pathways, consider HTA requirements, engage with industry, manage intellectual property, and design studies that can ultimately support development. These expectations reflect a legitimate shift towards impact-oriented research. Yet the system has not evolved at the same pace to provide the corresponding support. Training remains uneven, access to specialised expertise is fragmented, and entry points to regulatory or HTA dialogue are often unclear or perceived as burdensome. As a result, many researchers navigate this expanded role through informal networks or trial and error, with uneven outcomes.

This capability gap is compounded by the limited availability of shared infrastructures. Key assets such as registries, natural history studies, interoperable cohorts, endpoint platforms are widely recognised as foundational to rare disease progress. Yet they are too often funded as temporary projects rather than maintained as long-term system resources. When funding cycles end, maintenance becomes uncertain, governance weakens, and access conditions shift. What should function as stable backbone infrastructures instead operate under conditions of fragility.

Data illustrate this problem particularly clearly. The issue is not simply one of scarcity as valuable datasets exist across Europe, but they remain fragmented, unevenly standardised, difficult to discover, and insufficiently maintained for reuse. After projects conclude, there is rarely dedicated support for curation, documentation, or access brokerage. Data are generated but not systematically converted into shared assets that can support research, regulation, or care. A number of infrastructures, tools, and data platforms already exist across Europe, yet they remain underused. This is partly due to limited awareness among researchers, but also to fragmentation in access points, lack of integration into funding schemes, and insufficient incentives to adopt shared solutions over locally developed ones.

In this context, public-private partnerships (PPPs) are often presented as a solution. PPPs can play a critical role when they address specific gaps by bringing in missing expertise, supporting de-risking, or developing shared tools. However, their effectiveness depends heavily on design as if scope is too broad, too many partners, governance too complex, or ownership unclear, partnerships risk producing outputs without a clear pathway for sustainment or adoption. In some rare disease white spots, PPPs are unlikely to function as effective mechanisms for development. Where there is no plausible return on investment, industry participation will remain limited. In such cases, PPPs may still contribute to shared infrastructure or early-stage alignment but cannot be relied upon as primary drivers of therapeutic development.

Without reliable access to shared expertise, stable infrastructures, and sustained data resources, the burden placed on individual actors becomes disproportionate. Progress depends less on scientific potential than on the ability to navigate a system that lacks the necessary scaffolding. Without strengthening this backbone, improvements in funding or incentives alone are unlikely to deliver their full impact.

## Recommendations

- > **Make early interfaces with downstream actors easier to navigate and not relying on the development of these capacities independently by individual researchers' capacities.** This includes simpler and more visible routes to regulatory advice, HTA dialogue, and industry engagement, ideally at the stage where study design is still flexible.
- > **Invest in targeted, practice-oriented training.** Short, modular programmes focused on real-world application can help researchers better anticipate downstream requirements without expecting them to become specialists.
- > **Recognise and strengthen shared infrastructures as long-term assets.** Registries, cohorts, and endpoint platforms should be funded and governed as enduring resources, with clear responsibilities for maintenance and access over time.
- > **Encourage more structured and purpose-driven PPPs.** Partnerships should be designed around clearly identified gaps, with defined roles, realistic incentives, and explicit plans for ownership and continuation.
- > **More systematic matchmaking and shared-capability platforms could ensure more equitable access to resources across the ecosystem,** as progression currently depends on personal networks or ad hoc arrangements.



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