Recognizing & Rewarding the Value of Rare Disease Therapies

Global RD Policy Network

December 2025

Executive Summary

Rare diseases (RDs) are individually uncommon, but collectively they affect millions of people across the world and impose a disproportionate burden on patients, families, and health systems. Many are severe, progressive, and have high rates of mortality and morbidity. In recent decades, scientific advances and targeted policy incentives have expanded the pipeline of RD therapies, including treatments that can meaningfully alter the course of disease. Yet for many patients, regulatory approval is only the beginning of a longer path to access.

The central problem is that health technology assessment (HTA) and reimbursement systems in many economies remain poorly aligned with the clinical, evidentiary, and economic realities of RD therapies. RD therapies are often evaluated using HTA methods that are poorly matched to their evidentiary realities, causing uncertainty, unstable cost-effectiveness (CE) results, and systematic under-recognition of value elements such as severity, unmet need, equity, and caregiver burden. Even after regulatory approval, RD therapies often face fragmented HTA, pricing, and reimbursement processes that delay funded access, deepen inequities, and prevent innovation from translating into timely and equitable patient benefit. And lastly, the pricing of RD therapies is constrained by a structural mismatch between small markets and long-term therapeutic value on one hand, and payer systems built around short-term budgets and conventional affordability tests on the other, resulting in persistent access barriers and recurring disputes over what constitutes a reasonable price.

Policy Directions for Strengthening Lifecycle Evidence Generation & Data Infrastructure

1. Build evidence infrastructure around common data standards, interoperability, and governance
2. Tie evidence generation directly to reimbursement, reassessment, and managed access
3. Align pre-approval evidence planning with post-launch evidence needs

Policy Directions for Adapting Valuation Frameworks to Better Capture RD Value

1. Routinely present a complementary societal-perspective analysis alongside the reference case, supported by a transparent impact inventory
2. Apply explicit modifiers for severity & unmet need; use rarity cautiously rather than as a primary value driver
3. Use structured deliberation, and where appropriate multi-criteria decision analysis or similar tools, for value elements that are difficult to monetize robustly in conventional CE analysis
4. Treat valuation as a life-cycle process and schedule reassessment at defined evidence and pricing inflection points

Policy Directions for Strengthening Procedural Fairness, Transparency & Stakeholder Engagement in HTA

1. Formalize patient and clinician participation across the full appraisal life cycle, not only at the final consultation stage
2. Make deliberation traceable by publishing structured rationales that show how evidence and stakeholder input were weighed
3. Embed patients and clinicians in formal advisory or committee roles, with explicit safeguards for independence and consistency
4. Co-design post-launch evidence plans and managed access arrangements with the stakeholders who will have to implement them

Experience from APEC economies suggests that progress is possible, but implementation is uneven and operational and capacity constraints remain substantial. This makes deliberate, context-specific adaptation essential. In some settings, the first priority will be sophisticated managed entry and reassessment frameworks. In others, it will be establishing basic HTA functions, clearer criteria, and minimum viable real-world evidence capability. Irrespective of context, RD therapies should not be forced into frameworks that are poorly suited to the conditions under which they are developed and used. Health systems need fit-for-purpose approaches that are rigorous, transparent, and capable of balancing access, affordability, and incentives for continued innovation. More adaptive HTA, stronger evidence infrastructure, broader but disciplined valuation, and more meaningful stakeholder engagement can help reduce avoidable delay and ensure more equitable access.

Introduction

Rare diseases (RDs) are individually uncommon, but collectively they are a major public health and policy challenge. The World Health Organization defines a RD as a condition affecting fewer than one in 2,000 people within a WHO-defined region, and ICD-11 now recognizes thousands of such conditions.[1] Taken together, RDs are estimated to affect 6 to 8 percent of the global population. Most are genetic in origin, many emerge in infancy or childhood, and many are severe, progressive, and have high rates of mortality and morbidity. Their impact extends well beyond patients themselves, placing sustained clinical, emotional, and financial strain on families, health systems, and societies.

In recent decades, targeted policy interventions have helped stimulate research and development for RD therapies and have expanded the number of products reaching the market. For some patients, these therapies can alter the course of disease, prevent irreversible disability, extend survival, and improve quality of life. But scientific progress has outpaced the ability of many health systems to assess and pay for these therapies in a way that is timely, consistent, and fair. Most RDs still have no approved treatment, and where therapies do exist, access remains highly uneven across and within economies, especially in low- and middle-income settings.

This access gap reflects a deeper structural mismatch between the characteristics of RD therapies and the assumptions built into many health technology assessment (HTA) and reimbursement systems. RD evidence packages are often shaped by very small patient populations, incomplete natural history data, clinical heterogeneity, and reliance on non-traditional study designs. These features are often the inevitable consequence of developing therapies in conditions where conventional evidentiary models are impractical or impossible. Yet many HTA systems continue to evaluate these therapies using frameworks designed for larger populations, more mature comparative data, and more predictable treatment pathways.

That mismatch has important consequences. Conventional cost-effectiveness analysis (CEA) remains a valuable tool, but on its own it often struggles to capture the full value proposition of RD therapies. Standard approaches may understate benefits that unfold over long time horizons, particularly in pediatric-onset conditions. They may overlook caregiver burden, productivity effects, and other wider social consequences of disease. They may also fail to adequately reflect factors that many societies consider relevant in priority setting, including severity, profound unmet need, the absence of therapeutic alternatives, and the value of reducing uncertainty for patients facing devastating conditions. As a result, therapies that are clinically meaningful and socially important may appear to perform poorly when assessed against methods and thresholds that were not built with RDs in mind.

These tensions are becoming more urgent. Across APEC and other regions, governments are relying more heavily on HTA to guide pricing and reimbursement decisions as they seek to manage costs and sustain healthcare financing. At the same time, the pipeline for RD therapies is expanding, including advanced therapies with potentially transformative but uncertain long-term benefits. This is intensifying pressure on systems that must weigh legitimate concerns about affordability and evidentiary uncertainty against equally legitimate concerns about equity, timely access, and the societal value of continued innovation. The challenge is whether assessment frameworks are adequately equipped to recognize and reward value under the conditions in which these therapies are actually developed and used.

This paper examines why RD therapies pose recurring challenges for conventional HTA and reimbursement processes, and it sets out practical recommendations for improvement. Specifically, it considers how stronger data infrastructure, more adaptive evidence generation, broader and more transparent valuation frameworks, and more inclusive governance processes can help economies make better decisions about RD therapies. The objective is not to exempt these therapies from scrutiny, nor to weaken fiscal discipline, but rather to support HTA and reimbursement systems that are more analytically fit for purpose, more responsive to real-world conditions, and better able to balance access, affordability, and incentives for future innovation.

Challenges in Recognizing & Rewarding the Value of RD Therapies

Why Conventional HTA Methods Struggle to Capture the Value of RD Therapies

Key Issues

- Evidence scarcity driven by very small populations, clinical heterogeneity, limited natural history data, and frequent reliance on single-arm or otherwise nontraditional study designs
- Conventional cost-effectiveness methods are often poorly fitted to the evidence conditions typical of RD therapies and do not consistently capture broader sources of value such as severity, unmet need, caregiver effects, and other social value elements
- Standard discounting conventions, challenges with lifetime extrapolation, and thresholds developed outside the RD context can depress estimated value for therapies whose benefits are long term, potentially transformative, or concentrated in patients with severe diseases and no alternatives

Consequences

- Greater evidentiary uncertainty at the point of appraisal and heavier dependence on assumptions about comparators, long-term outcomes, and health-state utilities
- Higher and more unstable ICERs under conventional modeling assumptions, especially when benefits must be projected over long time horizons from immature evidence
- A persistent gap between what standard quantitative outputs capture and what many societies and policymakers may wish to recognize, particularly severity, unmet need, equity, and caregiver burden

The assessment of RD therapies exposes important methodological limits in the way many HTA systems quantify value. These limits emerge from the interaction of three factors: the evidence conditions under which RD therapies are developed, the structure of conventional cost-effectiveness (CE) models, and the decision rules used to translate modeled results into coverage recommendations.[2,3]

The first problem is evidentiary. Small patient populations, clinical/phenotypic heterogeneity, incomplete natural history data, and the absence of well-matched comparators often make conventional randomized evidence difficult or impossible to generate in RDs.[4,5] As a result, many RD therapies reach HTA with evidence packages that rely on single-arm trials, surrogate endpoints, historical controls, or shorter follow-up than would normally be preferred for mature comparative assessment.[6,7] Health-related quality of life (HRQoL) evidence is also often limited, whether because disease-specific instruments are lacking, utility mapping is weak, or follow-up is too short to capture the full trajectory of benefit.[8] The result is greater dependence on assumptions about long-term benefit, disease progression, and comparative effectiveness, which can materially shape CE estimates.[9]

The second problem is methodological fit. Conventional reference-case CEA, particularly when centered on cost per quality-adjusted life-year (QALY), is often poorly fitted to the evidence profile and value questions that arise in RDs, even though it remains a useful starting point for many decisions.[10,11] In practice, these models tend to work best when diseases have well-characterized natural histories, robust comparative data, and outcomes that are readily converted into validated utility estimates. RD appraisals often lack all three.[12,13] Just as important, the conventional QALY framework does not consistently reflect broader sources of value that are often central in RD policy discussions, including disease severity, lack of alternatives, caregiver burden, equity concerns, and other social value elements.[14,15] That gap helps explain why the formal model output may diverge from what patients, clinicians, and policymakers regard as a compelling therapeutic advance.

The third problem lies in decision rules. RD therapies often produce benefits that unfold over decades, especially in pediatric-onset conditions, yet those benefits must be estimated from immature data and then discounted back into present value using standard conventions that can substantially reduce the apparent value of long-term gains.[16,17] At the same time, many HTA systems still rely heavily on thresholds and evidentiary expectations developed outside the RD context, although some jurisdictions have introduced modifiers, adapted pathways, or specialized appraisal routes to address these challenges.[18,19] The issue is no longer whether RD appraisal is exceptional in practice but rather whether current adaptations are sufficient and consistently applied.

Taken together, these dynamics mean that RD therapies frequently enter appraisal with more uncertain evidence, more fragile comparative assumptions, and a narrower set of recognized value elements than therapies for more prevalent conditions.[20,21] Under standard methods, that combination can yield high or unstable incremental cost-effectiveness ratios (ICERs) and make positive recommendations harder to secure, particularly when committees are asked to apply conventional thresholds to severe conditions with no meaningful alternatives.[22,23] The consequence is that uncertainty is often penalized in ways that systematically disadvantage RD therapies relative to technologies developed under more favorable evidence conditions.[24,25]

For that reason, HTA should be adapted so that it remains rigorous while better reflecting the evidence realities and value judgments relevant to severe, high unmet need conditions. The literature and real-world case studies from APEC economies point toward several defensible directions, including greater use of deliberative appraisal, explicit treatment of severity and unmet need, broader recognition of caregiver and other non-health effects, and supplementary frameworks such as multi-criteria decision analysis (MCDA) or other structured approaches that can capture value elements not well represented in standard cost-per-QALY models.[26,27] Without that kind of adaptation, HTA systems will continue to under-recognize the value of many RD therapies before downstream reimbursement and budgetary constraints are even considered.

Systematic Barriers to Timely Reimbursement & Equitable Access

Key Issues

- Regulatory, HTA, pricing, and reimbursement processes are often insufficiently coordinated, so approval does not translate quickly into funded patient access
- Many systems still assess RD therapies through general pathways rather than fit-for-purpose routes, despite the need for greater flexibility, coordination, and RD-specific data infrastructure
- Financing architecture can become a second bottleneck after approval, including international reference pricing, repeated HTA referencing, budget constraints, payer fragmentation, and complex managed entry agreements

Consequences

- Delayed access after regulatory success, including in diseases where progression can reduce the benefit of waiting months or years for reimbursement
- Deepening inequities between economies and within them, driven by differences in reimbursement status, payer design, geography, and out-of-pocket burden
- Reduced real-world impact of innovation because approved therapies reach patients late, unevenly, or under highly restrictive conditions

Even when RD therapies secure regulatory approval and show meaningful clinical benefit, patient access is often delayed. In many systems, the major barrier is no longer authorization itself, but the sequence of appraisal, pricing, funding, and implementation decisions that follows. RD therapies therefore move into a bottleneck where fragmented post-approval processes determine whether patients can actually receive treatment, and on what terms.[28,29]

A first barrier is process misalignment. In many economies, regulatory review, HTA appraisal, price negotiation, and reimbursement listing remain sequential or only weakly coordinated, which extends the period between market authorization and funded access.[30,31] Both published and internal research show that most economies still do not operate a distinct end-to-end reimbursement process for drugs for RDs, although some have modified steps within standard pathways to improve access under uncertainty.[32,33] Where alignment is weak, the same therapy may face multiple rounds of evidence review, commercial negotiation, and administrative processing after approval, generating avoidable lag for patients with progressive conditions.[34]

A second barrier is uneven institutional capacity. Many HTA agencies and payers still evaluate RD therapies through general processes rather than through pathways specifically designed to handle sparse evidence, high unmet need, or the need for managed follow-up after launch.[35,36] Even in systems that show some flexibility, RD appraisals can take longer than appraisals for non-rare conditions, which means that procedural adaptability does not necessarily translate into speed.[37] In more fragmented systems, limited local pharmacoeconomic

expertise, the absence of standardized frameworks, and divided decision authority across ministries, insurers, or non-formulary processes can create further delays and inconsistencies in access.[38]

A third barrier is financing design. RD therapies often reach reimbursement review with high upfront budget implications and residual uncertainty about long-term outcomes, which can trigger prolonged negotiation, restrictive conditions of coverage, or delayed listing even when the clinical rationale is accepted.[39,40] Managed entry agreements (MEAs) can help address uncertainty and support earlier access, but they are complex to implement and their success depends on data systems, stakeholder coordination, and administrative capacity that many settings still lack.[41] In some economies, pricing and reimbursement are delayed further by international reference pricing rules or repeated payer negotiations, meaning that local access cannot proceed until pricing or appraisal milestones have been reached elsewhere.[42]

The cumulative effect is that a therapy may be approved, yet remain unavailable, delayed, geographically concentrated, or subject to conditions so narrow that population benefit is muted. For patients with progressive RDs, those delays can translate into lost health gains that cannot be fully recovered later. For health systems, the result is inefficient duplication, difficult budget planning, and access that is neither timely nor equitable.

Economic & Payment System Constraints in Funding RD Therapies

Key Issues

- Small addressable populations limit sales volume and complicate recovery of development, commercialization, and evidence-generation costs; for some products, specialized manufacturing and delivery add further cost pressure
- Annual budgeting and short time-horizon affordability tests are poorly aligned with therapies whose benefits may accrue over many years, especially one-time or potentially durable treatments
- Existing payment tools such as managed entry agreements, annuity-style payments, and amortization-inspired approaches can soften short-term budget pressure, but they do not fully resolve the structural mismatch between long-term value and one-year budget accountability

Consequences

- Persistent payer resistance to therapies with high upfront or high lifetime costs, even where the expected clinical benefit is substantial
- Continued controversy over what constitutes a reasonable price for RD therapies, particularly where conventional thresholds and annual budgets are used to judge products with very small markets and uncertain long-term outcomes
- Reliance on stop-gap financing arrangements that may enable access in selected cases but often add administrative complexity without correcting the underlying budget-design problem

The pricing of RD therapies is shaped less by any single cost driver than by the economics of very small markets, uncertain evidence, and payer systems that must make short-term funding decisions about products whose benefits may unfold over many years. Small eligible populations limit the volume over which manufacturers can recover development, commercialization, and post-launch evidence costs, which creates pressure for high per-patient prices even if development programs are not uniformly more expensive than those for non-orphan products.[43] In some cases, especially for advanced therapies, manufacturing, logistics, and administration are themselves unusually complex, adding further cost pressure and reinforcing payer concern about affordability.[44]

That does not mean price and budget impact are the same thing. RD therapies may have very high unit prices while still affecting only a small number of patients, but aggregate spending is not uniformly modest and cannot be assumed away on the basis of rarity alone.[45,46] Budget impact depends on the size of the eligible population, the duration of treatment, the number of products entering the budget, and whether spending is concentrated upfront or spread over time.[47] Chronic therapies can generate sustained cumulative expenditure over the lifetime of patients, while one-time or potentially durable gene therapies can produce a large upfront fiscal shock even when their long-term value proposition is strong.[48,49]

The central economic problem is therefore temporal mismatch. Many health systems budget annually and assess affordability over relatively short windows, while the claimed benefits of RD therapies, particularly

curative or near-curative treatments, may accrue over decades.[50,51] That mismatch can make a therapy appear fiscally disruptive even when its longer-term value is compelling. It also helps explain why therapies with similar lifetime value profiles can face very different reimbursement prospects depending on whether costs are incurred once, repeatedly, or in ways that fit existing budget categories.[52]

When markets are very small and reimbursement is uncertain, pricing debates become more intense because payers are being asked to fund "high-cost" therapies from annual budgets before long-term outcomes are fully observed.[53,54] Rather than asking whether a RD therapy is expensive, the question economies must ask and address is whether pricing and payment mechanisms are capable of handling a product whose value may be substantial but whose evidence and cash-flow profile sit awkwardly within conventional reimbursement structures.[55] Existing financing tools address this problem only partially. MEAs can help payers manage uncertainty and can support earlier access, but they require data infrastructure, clear outcome definitions, and substantial administrative coordination to function well in practice.[56] Spread payments and amortization-inspired approaches may ease short-term budget pressure, but they do not by themselves remove uncertainty, solve accounting constraints, or eliminate the need for sound appraisal and follow-up evidence.[57] In that sense, many current payment models are coping mechanisms rather than structural solutions.

Where pricing debates are prolonged and budgets remain rigid, reimbursement decisions become more contentious, launches in smaller markets become less attractive, and access is more likely to depend on *ad hoc* arrangements than on durable policy design.[58,59] Over time, this reinforces a familiar pattern, that therapies may be scientifically important and regulatorily approved, yet still reach patients late, unevenly, or under terms that mute their real-world impact. The underlying problem is the failure to align payment architecture with the economic profile of RD innovation.[60]

Directions for Better Recognizing & Rewarding the Value of RD Therapies

Strengthening Lifecycle Evidence Generation & Data Infrastructure

Strengthening the evidence base for RD therapies is essential because uncertainty must be reduced in a structured way over time. In RDs, the more realistic objective is a lifecycle evidence model that links pre-approval evidence planning, post-launch data collection, and scheduled HTA reassessment, so that reimbursement and pricing can evolve as evidence matures.[61,62] This directly addresses several of the barriers identified, including small samples, fragmented datasets, limited natural history information, and weak mechanisms for revisiting early decisions when better evidence becomes available. The direction should therefore be a lifecycle evidence ecosystem in which data generation is linked to real decisions. Well-designed registries and other real-world data sources can support natural history characterization, long-term outcome assessment, MEAs, and reassessment of earlier coverage decisions, but only if they are built around clear governance, fit-for-purpose data quality, and explicit decision use.[63,64] A more predictable evidence-to-decision pathway can also improve the functioning of coverage with evidence development (CED) and reduce the risk that therapies remain trapped indefinitely in a state of unresolved uncertainty.[65]

1. Build foundational evidence infrastructure around common data standards, interoperability, and governance

Ministries of health, HTA bodies, and RD programs should prioritize interoperable RD registries built on agreed minimum data sets, common terminology, and governance rules that make data usable across care, research, and assessment functions.[66,67] The literature and real-world case studies of APEC economies show that RD registries remain highly heterogeneous, with persistent weaknesses in terminological standardization, interoperability, quality management, and sustainability.[68,69] Registry governance should include strong clinical and patient participation, clear rules for access and custodianship, and ongoing quality assurance so that data can be trusted for regulatory, HTA, and payer use rather than serving only as descriptive repositories.[70,71] For many ultra-rare conditions, domestic sample sizes will remain too small to support robust long-term effectiveness or safety assessment. Cross-border data collaboration is therefore often necessary, especially for ultra-RDs, subgroup analysis, and long-horizon outcome tracking.[72,73] Existing regional and disease-specific collaborations should be used to pool data where feasible, provided that participating economies agree on common standards, privacy protections, and transparent governance.[74,75]

2. Tie evidence generation directly to reimbursement, reassessment, and managed access

Payers and HTA bodies should make post-launch evidence generation relevant to real-world decision-making from the outset. That means identifying the specific uncertainties that matter for coverage decisions, specifying the outcomes and timelines needed to resolve them, and linking those requirements to reassessment milestones rather than collecting data without a clear decision framework.[76,77] CED should therefore be used more systematically for RD therapies when early access is justified but uncertainty remains material, with explicit uncertainty statements, prespecified endpoints, defined study designs or registry protocols, reassessment dates, and consequences for noncompliance or failure to generate the required evidence.[78,79] Where data are collected routinely through electronic health records, claims, pharmacy datasets, mortality files, or patient-reported outcomes, those sources should be linked wherever legally and technically feasible so they can support periodic HTA reassessment and review of MEAs rather than remaining siloed across institutions.[80]

3. Align pre-approval evidence planning with post-launch evidence needs, and stage implementation for LMIEs

Regulators, HTA bodies, and payers should engage earlier in evidence planning so that RD development programs are not forced into a false choice between speed and relevance. In practice, this means earlier discussion with sponsors of endpoints, comparators, natural history data, registry use, and the role of surrogate measures or adaptive designs, together with a credible post-launch confirmation plan when residual

uncertainty is unavoidable.[81] Early regulatory-HTA dialogue will not remove uncertainty, but it can reduce avoidable misalignment between what is generated for approval and what will later be required for reimbursement.[82]

For LMIEs, the first objective should be to build a minimum viable architecture rather than to replicate the most complex registry systems used in high-income settings. Early investments should focus on practical building blocks such as agreed case definitions, minimum registry variables, unique identifiers where feasible, basic data quality procedures, and a small number of priority conditions or centers of excellence.[83] Partnerships with academic centers, patient organizations, and regional collaborative networks can help stand up pilot registries and shared analytic capacity while avoiding the exclusion of LMIE populations from real-world evidence generation altogether.[84] A staged approach is more credible than an all-at-once model, and it is more likely to produce data that are usable for care planning, policy development, and future HTA.[85]

Adapting Valuation Frameworks to Better Capture RD Value

HTA for RD therapies should not abandon conventional CEA, but it should adapt it. Standard HTA should be supplemented with broader value elements, explicit modifiers for selected normative priorities, and structured deliberation for factors that are difficult to monetize within a single ICER or cost-per-QALY ratio.[86,87] The objective is to use a valuation approach that better reflects the characteristics that repeatedly matter in RD decisions, especially severity, unmet need, caregiver spillovers, long-term benefit, and persistent uncertainty. The literature on RD valuation frameworks and societal preference studies points in that direction, while also showing that rarity alone is a weak basis for preferential treatment unless it is acting as a proxy for other concerns such as severity or lack of alternatives.[88],[89]

1. Routinely present a complementary societal-perspective analysis alongside the reference case, supported by a transparent impact inventory

A payer or healthcare-system perspective may remain the formal reference case, but RD appraisals should also include a complementary societal-perspective analysis so decision-makers can see value elements that fall outside direct healthcare spending, including caregiver time, productivity effects, education and employment impacts, and, where relevant, avoided disability or social service use.[90] Existing HTA guidelines mention some of these elements, but most do not recommend them consistently in the base case, which is one reason they are often acknowledged rhetorically but only weakly incorporated into decisions.[91] Because caregiver burden, productivity, severity, and quality-of-life effects can overlap, payers and HTA bodies should require a transparent impact inventory and explicit rules to minimize double counting rather than simply adding all social effects on top of the base-case result.[92]

2. Apply explicit modifiers for severity and unmet need, and use rarity cautiously rather than as a primary value driver

If payers and HTA bodies wish to go beyond a single universal threshold, the strongest basis for doing so is not rarity alone but severity, lack of effective alternatives, and in some cases proportional benefit or equity considerations.[93] Empirical reviews show that severity is more consistently preferred than rarity as a priority-setting criterion, and that public support for preferential treatment of RDs is driven mainly by severity and unmet need rather than prevalence by itself.[94] Any modifiers should therefore be pre-specified, limited to a small number of clearly justified criteria, and grounded either in empirical preference studies or explicit normative decisions rather than illustrative multipliers.[95]

3. Use structured deliberation, and where appropriate MCDA-type tools, for value elements that are difficult to monetize robustly in conventional CEA

Some elements that matter in RD decisions, including equity concerns, family spillovers, reduction in uncertainty, and insurance value, are not yet mature enough for routine, standardized monetization in every appraisal.[96] Insurance value is conceptually relevant because societies may value the availability of treatment for low-probability, high-consequence conditions, but current methods are still evolving and should be treated

as a structured deliberative input or piloted analytic element rather than a routine quantitative component of all RD appraisals.[97] MCDA and related structured approaches can help payers and HTA bodies make these judgments more explicit and transparent, especially when conventional CE outputs do not capture the full rationale for a recommendation.[98] Where such tools are used, decision-makers should record which qualitative or semi-quantitative factors influenced the recommendation and how they were weighed relative to the ICER, rather than invoking broader value elements informally without traceability.[99]

4. Treat valuation as a life-cycle process and schedule reassessment at defined evidence and pricing inflection points

Where uncertainty is expected to resolve over time, payers and HTA bodies should plan reassessment around predefined milestones such as post-authorization evidence readouts, MEA review points, major label expansions, or anticipated post-exclusivity pricing changes.[100] The emerging literature on life-cycle drug pricing shows that incorporating post-launch price evolution into CEA is methodologically feasible but complex, which is why reassessment rules should be transparent and tied to the evidence-generation infrastructure described in the previous subsection rather than applied *ad hoc*.[101] A life-cycle approach strengthens credibility because it allows value recognition to move in both directions: a therapy that performs better than expected can justify sustained or broader access, while one that underperforms can face revised conditions, narrower eligibility, or price adjustment.[102]

Strengthening Procedural Fairness, Transparency & Stakeholder Engagement in RD HTA

Multi-stakeholder engagement should be treated as a core part of RD HTA, not as an optional add-on at the end of appraisal. In RD decisions, high evidentiary uncertainty, significant ethical trade-offs, and the frequent absence of therapeutic alternatives increase the importance of processes that are transparent, inclusive, and procedurally fair.[103],[104] The aim should be to improve legitimacy, predictability, and consistency by making clear who participates, when they participate, what evidence they can provide, and how that input affects the final recommendation.[105] In RD HTA, better engagement can surface outcomes and burdens that are poorly captured in trials or generic HRQoL instruments, clarify what uncertainties matter most to patients and clinicians, and improve the design of post-launch evidence plans and reassessment pathways.[106],[107] Engagement does not guarantee agreement, and it should not displace analytic rigor, but it can make trade-offs more explicit and recommendations more defensible.[108]

1. Formalize patient and clinician participation across the full appraisal life cycle, not only at the final consultation stage

Payers and HTA bodies should publish a clear engagement framework that specifies when patient groups, clinical experts, and other stakeholders can contribute at scoping, evidence planning, appraisal, consultation, and reassessment stages.[109] Patient and clinician input should be gathered early enough to influence PICO framing, outcome selection, and uncertainty identification, rather than being confined to late-stage testimony after the analytic frame is already fixed.[110] In RD appraisals, this is particularly important because patient submissions often add information on caregiver burden, access barriers, mental health effects, and lived treatment goals that may otherwise be underrepresented in trial data or generic utility instruments.[111] Agencies should therefore provide plain-language guidance, standard submission templates, timelines, and proactive notifications when a therapy enters scoping or review so stakeholders can prepare usable input rather than react under severe time constraints.[112]

2. Make deliberation traceable by publishing structured rationales that show how evidence and stakeholder input were weighed

Transparency should extend beyond publishing a final yes-or-no decision. Payers and HTA bodies should issue structured public rationales that map the recommendation to explicit criteria such as clinical benefit, uncertainty, CE, severity or unmet need modifiers, patient input, and any conditions attached to reimbursement.[113] This matters because current practice often allows stakeholders to submit input without

clearly showing how that input affected the decision, which weakens trust and makes future participation less useful.[114] Where confidential discounts or MEAs limit price disclosure, payers and HTA bodies should still disclose non-price elements such as targeted uncertainties, outcomes to be measured, data-collection plans, reassessment dates, and decision triggers, because those components determine whether uncertainty is actually being resolved over time.[115] Public-facing committee summaries should also explain, in plain language, what evidence was persuasive, what remained uncertain, and why the decision-makers judged those uncertainties acceptable or unacceptable.[116]

3. Embed patients and clinicians in formal advisory or committee roles, with explicit safeguards for independence and consistency

Patient and clinician participation is most credible when roles are defined in advance rather than improvised case by case.[117] Depending on the institutional model, payers and HTA bodies can use committee membership, expert advisory panels, structured hearings, or consultation windows, but the rules should specify responsibilities, conflict-of-interest management, voting status where relevant, and how lived experience evidence is considered alongside clinical and economic evidence.[118] Conflict-of-interest rules are especially important in RD HTA because expertise is often concentrated in a small number of clinicians and centers, which makes participation indispensable but also potentially contested.[119] The right response to this dynamic is transparent disclosure, proportionate safeguards, and a clear method for documenting how experiential and clinical input informed deliberation.[120]

4. Co-design post-launch evidence plans and managed access arrangements with the stakeholders who will have to implement them

MEAs and real-world evidence plans often fail when endpoints are not meaningful to patients, are infeasible for clinicians to collect in routine care, or do not answer the uncertainties that matter to payers.[121] For that reason, payers and HTA bodies should involve clinicians and patient representatives, alongside manufacturers, when selecting outcomes, defining follow-up intervals, and setting reassessment triggers for RD therapies.[122] Early scientific advice or parallel consultation among regulators, HTA bodies, payers, and manufacturers should also be used more systematically so that study designs, registries, comparators, and endpoints are aligned with downstream reimbursement needs before avoidable misalignment is locked into the evidence package.[123] This is particularly relevant in RDs, where weak alignment between approval evidence and reimbursement evidence can add years of delay after authorization.[124]

Conclusion

RD therapies force health systems to confront a question that sits at the heart of modern health policy: how should societies assess and pay for treatments developed for small populations facing severe, often debilitating or fatal conditions under circumstances where uncertainty is unavoidable and conventional evidence standards are difficult to meet? The answer cannot be to abandon rigor. But it also cannot be to rely uncritically on assessment and reimbursement frameworks built for more common diseases, larger trials, and more predictable evidence packages. RD therapies are too often evaluated through processes that do not align with the realities of RD development, the full burden of rare conditions, or the broader value that effective treatment can deliver. Small studies, incomplete natural history data, high per-patient costs, and long-term or potentially transformative benefits are defining features of the field. When HTA and reimbursement systems fail to account for those features, therapies that may be clinically important and socially valuable are delayed, narrowly reimbursed, or left inaccessible altogether. For patients and families living with progressive, high-burden conditions, those delays can mean irreversible loss of function, avoidable deterioration, and missed windows for treatment.

This paper has argued that the way forward is adaptation rather than exceptionalism. Health systems need evidence pathways that are better designed for lifecycle learning, with stronger registries, clearer post-launch evidence requirements, and scheduled reassessment as data mature. They need valuation approaches that keep the discipline of CEA while making room for factors that matter in RD decisions, including severity, unmet need, caregiver burden, and other broader elements of value. They need appraisal and reimbursement processes that are more transparent, more predictable, and more inclusive of patient and clinician perspectives. And they need financing and access arrangements that can manage uncertainty without treating uncertainty itself as a reason for indefinite delay.

None of this is costless, and none of it is automatic. Adaptive HTA, MEAs, and post-launch evidence development require governance, analytic capacity, data infrastructure, and institutional discipline. Early experience from a range of economies, including some in APEC and other emerging markets, shows that progress is possible but uneven, and that one model cannot simply be imported everywhere. Economies can take practical, context-specific steps to make RD decision-making more credible and more functional. For LMIEs, the priority may be to build minimum viable capability first, including clear appraisal criteria, transparent deliberation, basic real-world evidence systems, and coordination across regulators, HTA bodies, and payers. Cross-border collaboration will also be essential. In many RDs, no single economy will generate sufficient evidence on its own. Joint registries, harmonized data standards, regional evidence partnerships, and pooled technical support can help reduce duplication, strengthen assessment, and improve the feasibility of managed access and reassessment over time.

Ultimately, recognizing and rewarding the value of RD therapies is not only a technical exercise in refining models and payment tools, but also a policy choice about whether health systems are willing to make their decision frameworks fit the realities of populations that have historically been underserved. Better HTA for RD therapies should lead to decisions that are more transparent, more consistent, and more responsive to both evidence and societal priorities. Health systems should be aiming for better scrutiny, fit-for-purpose evaluation, and a more credible balance between access, affordability, and sustained incentives to develop therapies for patients who still have far too few options.

References

[1] https://www.who.int/standards/classifications/frequently-asked-questions/rare-diseases
[2] Basu A, Thomas SK, Chapman RH, Spangler J. HTA Evidence in RDs: Just Rare or Also Special? Pharmacoeconomics. 2025 Nov;43(11):1271-1279. doi: 10.1007/s40273-025-01538-4. Epub 2025 Sep 9. PMID: 40924270; PMCID: PMC12534280.
[3] Grand TS, Ren S, Hall J, Åström DO, Regnier S, Thokala P. Issues, Challenges and Opportunities for Economic Evaluations of Orphan Drugs in RDs: An Umbrella Review. Pharmacoeconomics. 2024 Jun;42(6):619-631. doi: 10.1007/s40273-024-01370-2. Epub 2024 Apr 14. PMID: 38616217; PMCID: PMC11126517.
[4] Tingley K, Coyle D, Graham ID, Sikora L, Chakraborty P, Wilson K, Mitchell JJ, Stockler-Ipsiroglu S, Potter BK; Canadian Inherited Metabolic Diseases Research Network. Using a meta-narrative literature review and focus groups with key stakeholders to identify perceived challenges and solutions for generating robust evidence on the effectiveness of treatments for RDs. Orphanet J Rare Dis. 2018 Jun 28;13(1):104. doi: 10.1186/s13023-018-0851-1. PMID: 29954425; PMCID: PMC6022712.
[5] Grand et al., 2024.
[6] Drummond M, Ciani O, Fornaro G, Jommi C, Dietrich ES, Espin J, Mossman J, de Pouvourville G. How are health technology assessment bodies responding to the assessment challenges posed by cell and gene therapy? BMC Health Serv Res. 2023 May 13;23(1):484. doi: 10.1186/s12913-023-09494-5. PMID: 37179322; PMCID: PMC10182681.
[7] Abu Esba LC, Yousef CC, Khan MA, Balhareth S, Al-Omar HA, Al-Najjar A, Alkoraishi A, Alhammad AM, Almalki ZS, Altawil ES, Al Gain R, Ahmed M, Metwali H, Al Anizy L, Maraiki F, Al Jazairi A, Alhossan A, Al Harbi M, Almodaimegh H. Challenges in evaluation and reimbursement of drugs for RDs in Saudi Arabia: a Delphi expert consensus. J Pharm Policy Pract. 2025 Oct 28;18(1):2575040. doi: 10.1080/20523211.2025.2575040. PMID: 41195237; PMCID: PMC12584895.
[8] Grand et al., 2024.
[9] Drummond et al., 2023.
[10] Angelis A, Lange A, Kanavos P. Using health technology assessment to assess the value of new medicines: results of a systematic review and expert consultation across eight European countries. Eur J Health Econ. 2018 Jan;19(1):123-152. doi: 10.1007/s10198-017-0871-0. Epub 2017 Mar 16. PMID: 28303438; PMCID: PMC5773640.
[11] Basu et al., 2025.
[12] Grand et al., 2024.
[13] Tingley et al., 2018.
[14] Angelis et al., 2017.
[15] Drummond et al., 2023.
[16] Barman-Aksözen J, Hentschel N, Pettersson M, Schupp E, Granata F, Dechant C, Aksözen MH, Falchetto R. Fair Funding Decisions: Consistency of the Time Horizons Used in the Calculation of Quality-Adjusted Life Years for Therapies for Very RDs by the National Institute for Health and Care Excellence in England. Int J Environ Res Public Health. 2024 May 13;21(5):616. doi: 10.3390/ijerph21050616. PMID: 38791830; PMCID: PMC11121024.
[17] Garrison LP, Jackson T, Paul D, Kenston M. Value-Based Pricing for Emerging Gene Therapies: The Economic Case for a Higher Cost-Effectiveness Threshold. J Manag Care Spec Pharm. 2019 Jul;25(7):793-799. doi: 10.18553/jmcp.2019.18378. Epub 2019 Feb 20. PMID: 30784347; PMCID: PMC10397597.
[18] Basu et al., 2025.
[19] Hale G, Morris J, Barker-Yip J. Flexibility in assessment of RD technologies via NICE's single technology appraisal route: a thematic analysis. J Comp Eff Res. 2023 Nov;12(11):e230093. doi: 10.57264/cer-2023-0093. Epub 2023 Sep 19. PMID: 37724717; PMCID: PMC10690432.
[20] Grand et al., 2024.
[21] Drummond et al., 2023.
[22] Hale et al., 2023.
[23] Clarke S, Ellis M, Brownrigg J. The impact of rarity in NICE's health technology appraisals. Orphanet J Rare Dis. 2021 May 13;16(1):218. doi: 10.1186/s13023-021-01845-x. PMID: 33985575; PMCID: PMC8117316.
[24] Ibid.
[25] Basu et al., 2025.
[26] Chan M, Wang Y, Chuanchaiyakul T, Chavarina KK, Isaranuwatchai W, Teerawattananon Y. The relative importance of severity and rarity criteria in health resource allocation: an umbrella review. Int J Technol Assess Health Care. 2024 Nov 14;40(1):e54. doi: 10.1017/S0266462324004653. PMID: 39539097; PMCID: PMC11579674.
[27] Zelei T, Mendola ND, Elezbawy B, Németh B, Campbell JD. Criteria and Scoring Functions Used in Multi-criteria Decision Analysis and Value Frameworks for the Assessment of RD Therapies: A Systematic Literature Review.

Pharmacoecon Open. 2021 Dec;5(4):605-612. doi: 10.1007/s41669-021-00271-w. Epub 2021 May 18. PMID: 34003484; PMCID: PMC8611126.
[28] Feltmate K, Janiszewski PM, Gingerich S, Cloutier M. Delayed access to treatments for RDs: who's to blame? Respirology. 2015 Apr;20(3):361-9. doi: 10.1111/resp.12498. Epub 2015 Feb 26. PMID: 25722183.
[29] Stafinski T, Glennie J, Young A, Menon D. HTA decision-making for drugs for RDs: comparison of processes across countries. Orphanet J Rare Dis. 2022 Jul 8;17(1):258. doi: 10.1186/s13023-022-02397-4. PMID: 35804398; PMCID: PMC9264608.
[30] Feltmate et al., 2015.
[31] Stafinski et al., 2022.
[32] Ibid.
[33] Internal research.
[34] Feltmate et al., 2015.
[35] Stafinski et al., 2022.
[36] Hale et al., 2023.
[37] Ibid.
[38] Abu Esba et al., 2025.
[39] Facey KM, Espin J, Kent E, Link A, Nicod E, O'Leary A, Xoxi E, van de Vijver I, Zaremba A, Benisheva T, Vagoras A, Upadhyaya S. Implementing Outcomes-Based Managed Entry Agreements for RD Treatments: Nusinersen and Tisagenlecleucel. Pharmacoeconomics. 2021 Sep;39(9):1021-1044. doi: 10.1007/s40273-021-01050-5. Epub 2021 Jul 7. PMID: 34231135; PMCID: PMC8260322.
[40] Stafinski et al., 2022.
[41] Facey et al., 2021.
[42] Kluszczynski T, Nemeth B, Władysiuk M, Czech M, Kamusheva M, Fotin N, Rose S, Doležal T, Hren R. Optimizing Patient Access to Orphan Medicinal Products: Lessons from Central and Eastern Europe. J Mark Access Health Policy. 2025 May 26;13(2):24. doi: 10.3390/jmahp13020024. PMID: 40568380; PMCID: PMC12194612.
[43] Berdud M, Drummond M, Towse A. Establishing a reasonable price for an orphan drug. Cost Eff Resour Alloc. 2020 Sep 4;18:31. doi: 10.1186/s12962-020-00223-x. PMID: 32908456; PMCID: PMC7472708.
[44] Eichler HG, Kossmeier M, Zeitlinger M, Schwarzer-Daum B. Orphan drugs' clinical uncertainty and prices: Addressing allocative and technical inefficiencies in orphan drug reimbursement. Front Pharmacol. 2023 Jan 26;14:1074512. doi: 10.3389/fphar.2023.1074512. PMID: 36778019; PMCID: PMC9909264.
[45] Gombocz M, Vogler S. Public spending on orphan medicines: a review of the literature. J Pharm Policy Pract. 2020 Oct 13;13:66. doi: 10.1186/s40545-020-00260-0. PMID: 33062285; PMCID: PMC7552556.
[46] Eichler et al., 2023.
[47] Danzon PM. Affordability Challenges to Value-Based Pricing: Mass Diseases, Orphan Diseases, and Cures. Value Health. 2018 Mar;21(3):252-257. doi: 10.1016/j.jval.2017.12.018. PMID: 29566830.
[48] Ibid.
[49] Polek H, Janik J, Paterak E, Dabbous M, Pochopień M, Toumi M. The impact of amortization of gene therapies funding on the results and conclusions of CEMs and BIMs. J Mark Access Health Policy. 2023 Jul 10;11(1):2232648. doi: 10.1080/20016689.2023.2232648. PMID: 37440980; PMCID: PMC10334855.
[50] Danzon, 2018.
[51] Polek et al., 2023.
[52] Ibid.
[53] Berdud et al., 2020.
[54] Danzon, 2018.
[55] Eichler et al., 2023.
[56] Facey et al., 2021.
[57] Polek et al., 2023.
[58] Danzon, 2018.
[59] Eichler et al., 2023.
[60] Berdud et al., 2020.
[61] Dayer VW, Drummond MF, Dabbous O, Toumi M, Neumann P, Tunis S, Teich N, Saleh S, Persson U, von der Schulenburg JG, Malone DC, Salimullah T, Sullivan SD. Real-world evidence for coverage determination of treatments for RDs. Orphanet J Rare Dis. 2024 Feb 7;19(1):47. doi: 10.1186/s13023-024-03041-z. PMID: 38326894; PMCID: PMC10848432.

[62] Annemans L, Makady A. TRUST4RD: tool for reducing uncertainties in the evidence generation for specialised treatments for RDs. Orphanet J Rare Dis. 2020 May 26;15(1):127. doi: 10.1186/s13023-020-01370-3. PMID: 32456653; PMCID: PMC7251888.
[63] Hageman IC, van Rooij IALM, de Blaauw I, Trajanovska M, King SK. A systematic overview of RD patient registries: challenges in design, quality management, and maintenance. Orphanet J Rare Dis. 2023 May 5;18(1):106. doi: 10.1186/s13023-023-02719-0. PMID: 37147718; PMCID: PMC10163740.
[64] Kodra Y, Weinbach J, Posada-de-la-Paz M, Coi A, Lemonnier SL, Van Enckevort D, Roos M, Jacobsen A, Cornet R, Ahmed SF, et al. Recommendations for Improving the Quality of RD Registries. International Journal of Environmental Research and Public Health. 2018; 15(8):1644. https://doi.org/10.3390/ijerph15081644
[65] Annemans & Makady, 2020.
[66] Bernardi FA, Mello de Oliveira B, Bettiol Yamada D, Artifon M, Schmidt AM, Machado Scheibe V, Alves D, Félix TM. The Minimum Data Set for RDs: Systematic Review. J Med Internet Res. 2023 Jul 27;25:e44641. doi: 10.2196/44641. PMID: 37498666; PMCID: PMC10415943.
[67] Rémy Choquet, Meriem Maaroufi, Albane de Carrara, Claude Messiaen, Emmanuel Luigi, Paul Landais, A methodology for a minimum data set for RDs to support national centers of excellence for healthcare and research, Journal of the American Medical Informatics Association, Volume 22, Issue 1, January 2015, Pages 76–85, https://doi.org/10.1136/amiajnl-2014-002794
[68] Bernardi et al., 2023.
[69] Internal research.
[70] Kodra et al., 2018.
[71] Boulanger V, Schlemmer M, Rossov S, Seebald A, Gavin P. Establishing Patient Registries for RDs: Rationale and Challenges. Pharmaceut Med. 2020 Jun;34(3):185-190. doi: 10.1007/s40290-020-00332-1. PMID: 32215853; PMCID: PMC7286934.
[72] Hageman et al., 2023.
[73] Boulanger et al., 2020.
[74] Choquet et al., 2015.
[75] Gonzaga-Jauregui C, Salazar C, MacDonald J, Reichardt JKV, Groft SC. ERCAL, a regional initiative for RDs in Latin America and the Caribbean. Rare Dis Orphan Drugs J. 2024;3:6. http://dx.doi.org/10.20517/rdodj.2023.48
[76] Annemans & Makady, 2020.
[77] Dayer et al., 2024.
[78] Ibid.
[79] Ollendorf D, Henshall C, Phillips M, Synnott P, Sansom L, Tunis S. Putting meat on the bone: how to fast-track innovative medicines to those who need them and generate data to justify continued use. Health Aff Sch. 2024 Aug 9;2(8):qxae095. doi: 10.1093/haschl/qxae095. PMID: 39161949; PMCID: PMC11332269.
[80] Bernardi et al., 2023.
[81] Wonder M, Backhouse ME, Hornby E. Early scientific advice obtained simultaneously from regulators and payers: findings from a pilot study in Australia. Value Health. 2013;16(6):1067-1073. doi:10.1016/j.jval.2013.07.007
[82] Ibid.
[83] Rodrigues G, Poletto E, E Vairo FP, Baldo G. Basic and translational research in rare diseases in low- and middle-income countries: challenges and solutions. J Community Genet. 2025;16(4):421-423. doi:10.1007/s12687-024-00759-y
[84] Ibid.
[85] Hageman et al., 2023.
[86] Muir JM, Radhakrishnan A, Freitag A, Ozer Stillman I, Sarri G. Reconstructing the value puzzle in health technology assessment: a pragmatic review to determine which modelling methods can account for additional value elements. Front Pharmacol. 2023;14:1197259. Published 2023 Jul 13. doi:10.3389/fphar.2023.1197259
[87] Zelei T, Mendola ND, Elezbawy B, Németh B, Campbell JD. Criteria and Scoring Functions Used in Multi-criteria Decision Analysis and Value Frameworks for the Assessment of Rare Disease Therapies: A Systematic Literature Review. Pharmacoecon Open. 2021;5(4):605-612. doi:10.1007/s41669-021-00271-w
[88] Vásquez P, Hall L, Merlo G. Societal Preferences in Health Technology Assessments for Rare Diseases and Orphan Drugs: A Systematic Literature Review of New Analytic Approaches. Value in Health Regional Issues. 2024;44:101026-101026. doi:https://doi.org/10.1016/j.vhri.2024.101026
[89] Dabbous, O., Chachoua, L., Aballéa, S. et al. Valuation of Treatments for Rare Diseases: A Systematic Literature Review of Societal Preference Studies. Adv Ther 40, 393–424 (2023). https://doi.org/10.1007/s12325-022-02359-z

[90] Breslau RM, Cohen JT, Diaz J, Malcolm B, Neumann PJ. A review of HTA guidelines on societal and novel value elements. Int J Technol Assess Health Care. 2023;39(1):e31. Published 2023 May 25. doi:10.1017/S026646232300017X
[91] Ibid.
[92] Vasquez et al., 2024.
[93] Chan et al., 2024.
[94] Ibid.
[95] Zelei et al., 2021.
[96] Muir et al., 2023.
[97] Ibid.
[98] Vasquez et al., 2024.
[99] Breslau et al., 2023.
[100] Puls M, Horscroft J, Kearns B, et al. Challenges of Incorporating Life Cycle Drug Pricing in Cost-Effectiveness Models: A Review of Methods and Modeling Suggestions. Value Health. 2024;27(7):978-985. doi:10.1016/j.jval.2024.03.006
[101] Ibid.
[102] Basu et al., 2025.
[103] Bond K, Stiffell R, Ollendorf DA. Principles for deliberative processes in health technology assessment. International Journal of Technology Assessment in Health Care. 2020;36(4):445-452. doi:10.1017/S0266462320000550
[104] Oortwijn W, Husereau D, Abelson J, et al. Designing and Implementing Deliberative Processes for Health Technology Assessment: A Good Practices Report of a Joint HTAi/ISPOR Task Force. Value in Health. 2022;25(6):869-886. doi:https://doi.org/10.1016/j.jval.2022.03.018
[105] Carter D, Laka M, Gao Y, Choi O, Tamblyn D, Merlin T. Engaging stakeholders along health technology assessment pathways: a scoping review of international practice. Int J Technol Assess Health Care. 2025;41(1):e69. Published 2025 Sep 30. doi:10.1017/S0266462325100494
[106] Gentilini A, Rana A. How are patient inputs considered in HTA? A thematic document analysis of NICE ultra-rare disease appraisals. Eur J Health Econ. 2025;26(6):945-968. doi:10.1007/s10198-024-01748-1
[107] Lopez Gousset V, Silveira Silva A, Holtorf A-P, Toledo-Chávarri A, Single A. The three-domain impact framework for characterizing impact of patient involvement in health technology assessment. International Journal of Technology Assessment in Health Care. 2024;40(1):e52. doi:10.1017/S0266462324000400
[108] Bond et al., 2020.
[109] Carter et al., 2025.
[110] Tafuri G, Lucas I, Estevão S, et al. The impact of parallel regulatory-health technology assessment scientific advice on clinical development. Assessing the uptake of regulatory and health technology assessment recommendations. Br J Clin Pharmacol. 2018;84(5):1013-1019. doi:10.1111/bcp.13524
[111] Gentilini et al., 2025.
[112] Wale, J.L., Thomas, S., Hamerlijnck, D. et al. Patients and public are important stakeholders in health technology assessment but the level of involvement is low – a call to action. Res Involv Engagem 7, 1 (2021). https://doi.org/10.1186/s40900-020-00248-9
[113] Bond et al., 2020.
[114] Carter et al., 2025.
[115] Facey et al., 2021.
[116] Botwright S, Sittimart M, Chavarina KK, et al. Good Practices for Health Technology Assessment Guideline Development: A Report of the Health Technology Assessment International, HTAsiaLink, and ISPOR Special Task Force. Int J Technol Assess Health Care. 2025;40(1):e74. Published 2025 Jan 6. doi:10.1017/S0266462324004719
[117] Wale et al., 2021.
[118] Oortwijn et al., 2022.
[119] Gentilini et al., 2025.
[120] Bond et al., 2020.
[121] Facey et al., 2021.
[122] Gousset et al., 2024.
[123] Tafuri et al., 2018.
[124] Ibid.