Alternative Evidence Generation Approaches for Rare Diseases: Addressing HEOR and Healthcare Decision-Making Challenges

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Introduction

- Generating robust evidence to inform healthcare value and access decisions in rare diseases can present persistent methodological and practical challenges, primarily due to small, heterogeneous populations, limited longitudinal data, and rapidly evolving treatment paradigms that often outpace conventional evidence generation approaches.[1-2]
- In these contexts, large scale health economics and outcomes research (HEOR) studies, such as discrete-choice experiments (DCEs) or large-scale real-world evidence studies, are often not feasible, underpowered, or misaligned with the pace of therapeutic innovation, where rapidly emerging treatments and evolving standards of care can outpace the timelines of conventional research.[3-4]
- Such constraints highlight the need for fit-for-purpose, adaptable evidence approaches that integrate stakeholder perspectives while maintaining scientific rigour.[5-6]
- We therefore sought to review existing evidence and methodological literature with the aim of developing and operationalising a modular evidence generation framework tailored for rare diseases, designed to support patient-centred, payer-relevant, and regulator-credible evidence generation that complements conventional HEOR and healthcare decision-making (HCDM) approaches.[7-8]

Methods

- A focused evidence search (2018–2025 publication period) of peer-reviewed literature, health technology assessment (HTA) submissions, and conference proceedings was conducted to identify recurring methodological challenges in rare disease evidence generation across major HTA jurisdictions, including the United Kingdom (National Institute for Health and Care Excellence [NICE], Scottish Medicines Consortium [SMC]), European Union (Haute Autorité de Santé [HAS], Agenzia Italiana del Farmaco [AIFA], Gemeinsamer Bundesausschuss [G-BA], Zorginstituut Nederland [ZIN]), and selected international comparators (Canadian Agency for Drugs and Technologies in Health [CADTH], Institute for Clinical and Economic Review [ICER], Pharmaceutical Benefits Advisory Committee [PBAC]).[1,7,9,11-13]
- Findings were synthesised thematically to map data limitations, feasibility barriers, and stakeholder-specific evidence needs.[2,4,15]
- A modular framework was then iteratively designed and refined through internal consultation with HEOR methodologists and rare disease specialists to ensure relevance across the product lifecycle and alignment with patient, payer, and regulatory perspectives.[5-6,14,19]
- Conceptual validation was performed using illustrative case mapping across ultra-rare metabolic and immunologic disorders to test applicability, scalability, and completeness.[3-4,10,21]

Figure 1. Overview of methods for modular framework development

1. Targeted evidence search (2018–2025 publication period)
Identify key methodological challenges and data limitations in rare disease evidence generation.

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2. Thematic synthesis
Group findings into themes: data gaps, feasibility barriers, stakeholder needs.

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3. Framework design
Develop modular framework structure informed by HEOR best practice.

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4. Conceptual validation (illustrative case mapping)
Apply framework to ultra-rare case examples (e.g., metabolic and immunologic disorders) to assess relevance, scalability, and completeness.

HEOR: Health economics and outcomes research.

Results

1. Identified challenges in rare disease evidence generation

The evidence search confirmed multiple recurring barriers to robust value demonstration:

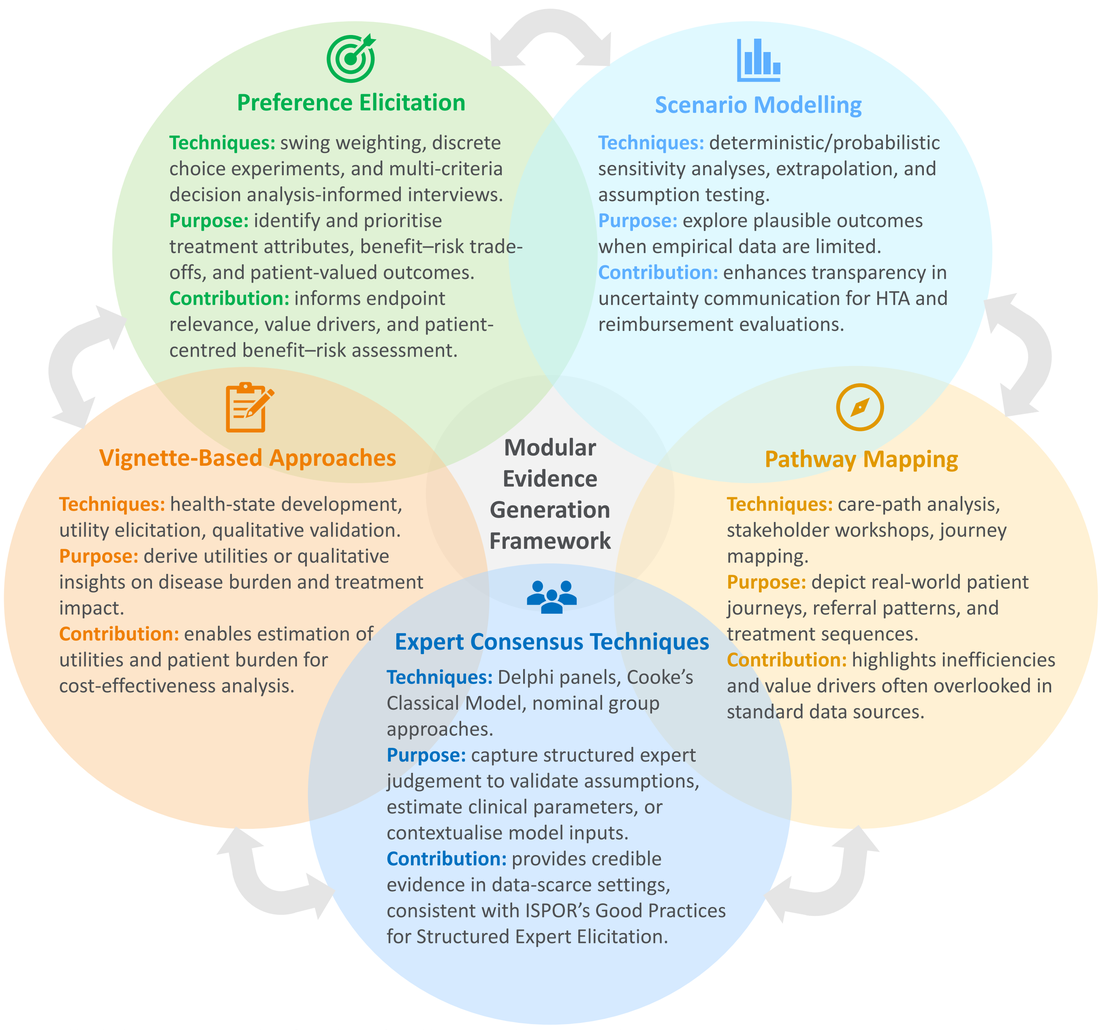
- Small and heterogeneous populations limiting statistical power and external validity.[1-3,15]
- Uncertain or delayed clinical outcomes restricting the feasibility of conventional endpoints.[4,9,17]
- Fragmented real-world data across registries and geographies, limiting longitudinal follow-up.[2,7,18]
- Insufficient patient and caregiver involvement in defining outcomes of relevance to quality of life.[1,6,19]
- Divergent HTA and payer evidence expectations, such as requirements for comparative effectiveness, robust survival modelling, or quality of life (QoL) data, often require evidence that cannot be feasibly generated in rare disease contexts.[7-8,13,20]

Together, these issues underscore the need for a scalable, modular framework to generate credible, decision-relevant evidence when traditional methods are unviable, inappropriate, or insufficient to demonstrate value in rare disease contexts.

2. Development of a modular framework for alternative evidence generation

Insights from the evidence review informed the development of a five-module framework (see **Figure 2**) integrating adaptable, complementary approaches to evidence generation under data constraints (see **Table 1**).[5-8,14,19]

Figure 2. Modular evidence generation framework



HTA: Health technology assessment; ISPOR: The Professional Society for Health Economics and Outcomes Research

Results (continued)

Table 1. Mapping the framework to key evidence needs

Evidence Gap/ Challenge	Alternative Approach/ Module	Description/ Example	Value Added for HEOR and HTA
Lack of patient-centred outcomes	Preference Elicitation	Swing weighting or best–worst scaling to identify treatment attributes and outcomes that matter most to patients and caregivers	Prioritises meaningful outcomes for patient-focused drug development and payer communication
Uncertainty around long-term outcomes and limited extrapolation data	Scenario Modelling	Sensitivity analyses and exploratory projections addressing uncertainty in disease progression and treatment benefit	Improves robustness of economic evaluations and supports conditional reimbursement frameworks
Small and heterogeneous populations limit feasibility of RCTs	Expert Consensus	Delphi panels, structured advisory boards or SEEs used to validate assumptions, define endpoints, and estimate clinical parameters	Provides credible inputs where empirical data are limited; enhances transparency and reproducibility of model assumptions
Limited HRQoL or utility data for rare disease populations	Vignette-Based Approaches	Development of health-state vignettes valued by patients or general population to derive utility estimates	Enables QALY estimation where direct HRQoL data are unavailable; increases comparability across indications
Fragmented and non-standardised patient pathways	Pathway Mapping	Mapping diagnostic and treatment journeys through multi-stakeholder workshops to visualise care variation and burden	Identifies real-world inefficiencies, unmet needs, and value drivers supporting payer and HTA narratives

HEOR: Health economics and outcomes research; HRQoL: Health related quality of life; HTA: Health technology assessment; QALY: Quality-adjusted life year; RCT: Randomised controlled trial; SEE: Structured expert elicitation.

3. Illustrative application:

- To demonstrate the practical application of the modular framework, it was applied to an ultra-rare kidney metabolic disease characterised by heterogeneous clinical presentation, where limited clinical evidence and uncertainty regarding patient-relevant outcomes pose major challenges to value demonstration.[10,20]
- Given the ultra-rare nature of this disease, conventional preference elicitation methods, such as DCEs, may not be methodologically feasible due to small sample sizes and high cognitive burden.[2,5]
- Swing weighting interviews could therefore be selected as a mixed-methods approach to capture patient preferences in a more narrative and accessible manner.[5-6]
- This method allows participants to rank or rate the importance of "swings" between the worst and best levels of key treatment attributes (e.g., frequency of dialysis, fatigue severity, or proteinuria control).[5-6]
- Compared with DCEs, swing interviews offer greater flexibility for in-depth discussion, enabling exploration of the rationale behind preferences and contextual factors that are difficult to quantify in conventional quantitative approaches.[5] This also reduces respondent fatigue and mitigates the impact of varying levels of health literacy, improving data quality and inclusivity in ultra-rare populations.[6]
- Insights generated through the swing weighting interview approach can then be triangulated across complementary modules of the framework, including expert consensus techniques (e.g., Delphi panels or structured expert elicitations [SEEs]) to validate key outcomes, vignette-based approaches (e.g., patient-informed health state vignettes) to contextualise disease burden, and pathway mapping (e.g., mapping diagnostic and treatment pathways) to identify evidence gaps.[3,5] Scenario modelling (e.g., exploring variations in patient-valued attributes) can then be used to assess the impact of these outcomes on projected treatment benefit and economic value.[3,5-6,14]
- This illustrative application highlights how qualitative preference elicitation, supported by expert and modelling modules, can operationalise the framework in rare diseases with limited data availability, therefore enhancing transparency, patient relevance, and decision-making value.[1,2,5,19]

4. Application across the rare disease evidence landscape

The following section demonstrates how the modular framework can be applied across the rare disease evidence landscape, illustrating its relevance to key stakeholders at each stage of the product lifecycle. **Table 2** summarises the role of each module in supporting patients, payers, regulators, and clinicians. When considering application across stakeholder types, the following recommendations should be considered:

- Patients and Caregivers: Engage directly through preference elicitation and indirectly through qualitative interviews that inform vignette development, ensuring that outcomes reflect lived experience.[1,6,19]
- Payers and HTA Bodies: Use scenario modelling and expert elicitation to characterise uncertainty and strengthens confidence in value claims.[3,7-8,15,20]
- Regulators: Leverage consensus and qualitative evidence to address residual post-approval data gaps or justify label expansions.[9-12]
- Clinicians: Participate in Delphi panels and review patient-informed vignettes to ensure clinical validity, contextualise real-world management, and support evidence-based practice.[5-6,14]

Importantly, modular techniques can be used in conjunction, for example by integrating patient-derived preferences , expert-elicited parameters , and scenario modelling outputs to triangulate insights, enhance robustness, and strengthen alignment between stakeholder perspectives.

This lifecycle-oriented design facilitates cross-stakeholder alignment, supporting consistent, patient-centred decision-making across jurisdictions.

Table 2. Application across the evidence landscape

Stakeholder	Early Development	Pre-launch	HTA Submission	Post-launch
Patient	Preference elicitation to identify valued attributes of care or interventions	Vignette testing for HRQoL and utility refinement	Input on outcomes in HTA submissions	Pathway mapping to assess ongoing unmet need
Clinician	Expert consensus and SEE to define endpoints and feasibility	Swing weighting to prioritise outcomes	Scenario modelling to validate clinical assumptions	Pathway mapping to assess care optimisation
Regulator	Scenario modelling to explore uncertainty	Expert consensus on endpoints and comparators	Application of validated evidence modules to support regulatory alignment	Continuous evidence adaptation post-approval
Payer	Pathway mapping to define system value and resource impact	Preference elicitation to understand treatment drivers	Scenario modelling and budget impact analysis	Expert consensus to interpret real-world effectiveness

HRQoL: Health related quality of life; HTA: Health technology assessment; SEE: Structured expert elicitation.

Conclusions

- The modular framework provides a scalable, context-appropriate solution for evidence generation in rare diseases, complementing existing The Professional Society for Health Economics and Outcomes Research (ISPOR) good practice guidance on evidence generation solutions such as, structured expert elicitation, multi-criteria decision analysis (MCDA), and patient preference studies.[1,5-6,13,18]
- By integrating qualitative, hybrid, and expert-driven methods, the framework generates robust, actionable insights where conventional designs are unviable, inappropriate, or insufficient to demonstrate value in rare disease contexts.[2,5,7]
- It advances methodological innovation by recognising that "one-size-fits-all" evidence strategies are insufficient in rare disease contexts.[3,8-9,14]
- By systematically combining these modules, stakeholders can generate actionable insights that support payer engagement, inform HTA submissions, and improve healthcare decision-making in rare and ultra-rare diseases.[1,7-8,12-13,19]
- Ultimately, this framework makes HEOR evidence more credible, patient-relevant, and actionable, supporting equitable access to innovative therapies. [7,10-12]
- Future work will focus on applying case studies across diverse rare conditions to validate and refine the framework for practical implementation in HTA and payer engagement.[1-3]

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