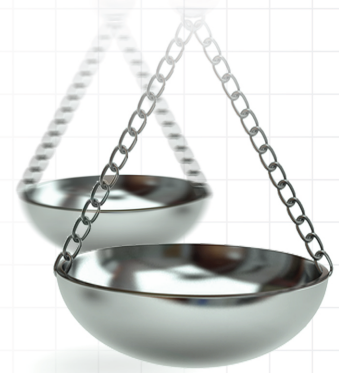




Navigating the unknown: how to best 'reflect' standard of care in indications without a dedicated treatment pathway in health technology assessment submissions

Journal of **Comparative Effectiveness Research**

Grammati Sarri¹, Maria Rizzo¹, Sheela Upadhyaya[‡], Victoria Federico Paly² & Luis Hernandez^{*,2}

¹Cytel, Inc., London, UK

²Takeda Pharmaceuticals America, Inc., Lexington, MA, USA

*Author for correspondence: Tel.: +1 781 482 9222; luis.hernandez3@takeda.com

[‡]Employed by the National Institute for Health and Care Excellence when this manuscript was drafted.

There is an urgent need for expedited approval and access for new health technologies targeting rare and very rare diseases, some of which are associated with high unmet treatment needs. Once a new technology achieves regulatory approval, the technology needs to be assessed by health technology assessment (HTA) bodies to inform coverage and reimbursement decisions. This assessment quantitatively examines the clinical effectiveness, safety and/or economic impact of the new technology relative to standard of care (SoC) in a specific market. However, in rare and very rare diseases, the patient populations are small and there is often no established treatment pathway available to define 'SoC'. In these situations, several challenges arise to assess the added benefit of a new technology – both clinically and economically – due to lack of established SoC to guide an appropriate comparator selection. These challenges include: How should 'SoC' be defined and characterized in HTA submissions for new technologies aiming to establish new treatment standards? What is usual care without an established clinical pathway? How should the evidence for the comparator 'SoC' (i.e., usual care) arm be collected in situations with low patient representation and, sometimes, limited disease-specific clinical knowledge in certain geographies? This commentary outlines the evidence generation challenges in designing clinical comparative effectiveness for a new technology when there is a lack of established SoC. The commentary also proposes considerations to facilitate the reliable integration of real-world evidence into HTA and decision-making based on the collective experience of the authors.

First draft submitted: 26 September 2023; Accepted for publication: 12 December 2023; Published online: 16 January 2024

Keywords: health technology assessment • oncology • rare diseases • real-world evidence • single-arm trials

Rare or very rare diseases are characterized by low prevalence (e.g., <200,000 in the US [1], one in 2000 in the European Union [EU] and in the UK [2,3]) or very low prevalence (<1 in 50,000) [4,5], respectively. These diseases are often life-threatening or chronically debilitating and are commonly caused by a genetic predisposition [2]. During the last decade, several regulatory and reimbursement developments have provided incentives for manufacturers to invest in innovative health technologies to derive benefit in areas of high unmet need for small groups of patients, while acknowledging the difficulties in generating evidence for these diseases [6–9].

The challenges of evidence generation in rare and very rare diseases are multifaceted and health technologies targeting such diseases encounter obstacles in demonstrating patient benefit [10]. Beyond the difficulties associated with small patient numbers, formulating the natural history of the disease can also be problematic due to heterogeneity in the disease presentation, lack of understanding of this heterogeneity, limited disease-specific clinical knowledge in some geographies, and discrepancies in the availability of diagnostic technologies across markets [11]. In addition, there may be a greater emphasis to establish surrogate end points to accelerate market authorization, potentially limiting the collection of long-term follow-up evidence from clinical studies such as mortality, morbid-



ity, and quality of life and, thus, creating market access and reimbursement challenges for medicines targeting these diseases [12]. These reasons have impelled some health technology assessment (HTA) bodies to develop frameworks and criteria for decision-making specifically targeting rare or very rare diseases (e.g., expanding value elements, statements of willingness to accept more uncertainty in the evidence base, reimbursement linked to future evidence generation) [7,13–16]. The evidence generation challenges in rare and very rare diseases during HTA occur alongside the pricing and affordability pressures on healthcare systems with the rapid increase in regulatory approval of medicines for these diseases. Different rules such as decision modifiers (e.g., severity of disease), willingness-to-pay thresholds and alternative reimbursement rules have been also proposed [17–20]. These pricing and affordability challenges have been widely outlined elsewhere and are beyond the scope of this commentary [10,16,21–24]. We instead aim to highlight a topic that has received less attention in HTAs – specifically to outline the practical challenges in evidence generation and HTA processes for new health technologies targeting rare and very rare indications when there is a lack of an established treatment care pathway (i.e., standard of care [SoC]) and the new technology aims to establish new treatment standards. This is usually the case when new treatments are tested in single-arm trials; methodological issues and HTA concerns related to confounding and bias in building external control arms are widely covered in recent guidance (US FDA [25], European Medicines Agency [26], National Institute for Health and Care Excellence [NICE] [27], Canadian Agency for Drugs and Technologies in Health [28], Haute Autorité de Santé [29]) and are not covered in this commentary.

When there is no established clinical pathway, commonly seen in rare and very rare conditions, patients are often treated with diverse (mainly off-label) therapies in clinical practice, usually determined by individual physicians' choice [30,31]. However, reliable information to describe these treatment patterns and their outcomes may be limited, which poses further challenges as these off-label therapies may be seen as comparators from a statutory perspective during HTAs to establish the most appropriate 'SoC' against which to estimate the added clinical benefit and economic impact of the new technology under assessment [12,32,33]. Although HTA bodies may offer manufacturers some flexibility to generate evidence in these situations, no guidance, so far, has been issued to determine considerations when no standard clinical pathway exists or to outline the trade-offs between different data sources that can inform the comparator arm and ensure patient generalizability [34]. In this commentary, we first outline the main challenges in identifying the evidence for the SoC arm to support comparative clinical and cost-effectiveness assessments for new health technologies in these circumstances. In the second part, we provide considerations that may facilitate future strategies for manufacturers and decision-makers to robustly address these challenges in HTA submissions (Figure 1).

HTA evidence generation & process challenges for indications with no established SoC

Challenges in systematic identification of comparator evidence

Systematic and unbiased identification and synthesis of relevant evidence for a health technology under assessment and its comparators is the cornerstone of the HTA process. However, when there is no established SoC, the evidence on treatments received by the target population in clinical practice is usually scarce or does not exist, or may be obtained from small observational studies with limited representation of the target and/or local populations, potentially compromising the validity, generalizability, and precision of comparative clinical effectiveness results [35]. Considerations about the clinical validity and appropriateness to expand the population criteria across multiple areas such as eligibility, temporality, population representation across geographies, and comparability with the population studied in the clinical trial of the health technology under assessment need to be defined a-priori when the research questions are framed. Expansion of selection criteria in systematic literature reviews of treatments for rare and very rare diseases to allow wider coverage of the population of reference (e.g., use of umbrella terms for disease classification, proxy populations) and specific challenges in conducting such reviews for rare diseases have been previously highlighted [36]. However, to what extent is it clinically valid and appropriate, and acceptable by HTA bodies, to use evidence from a broader patient population as a proxy for one with a rare or very rare disease and what is the appropriate threshold criteria to consider a proxy population 'comparable enough' with the target population?

Even when some evidence is available for the treatments used off label for the target rare or very rare indication, differences with the population studied in the clinical trial of the health technology under assessment across geographies, heterogeneity in data sources that may preclude data pooling to allow increase of comparator's sample size or patient heterogeneity can pose serious threats in ensuring a systematic approach in literature reviews is followed.

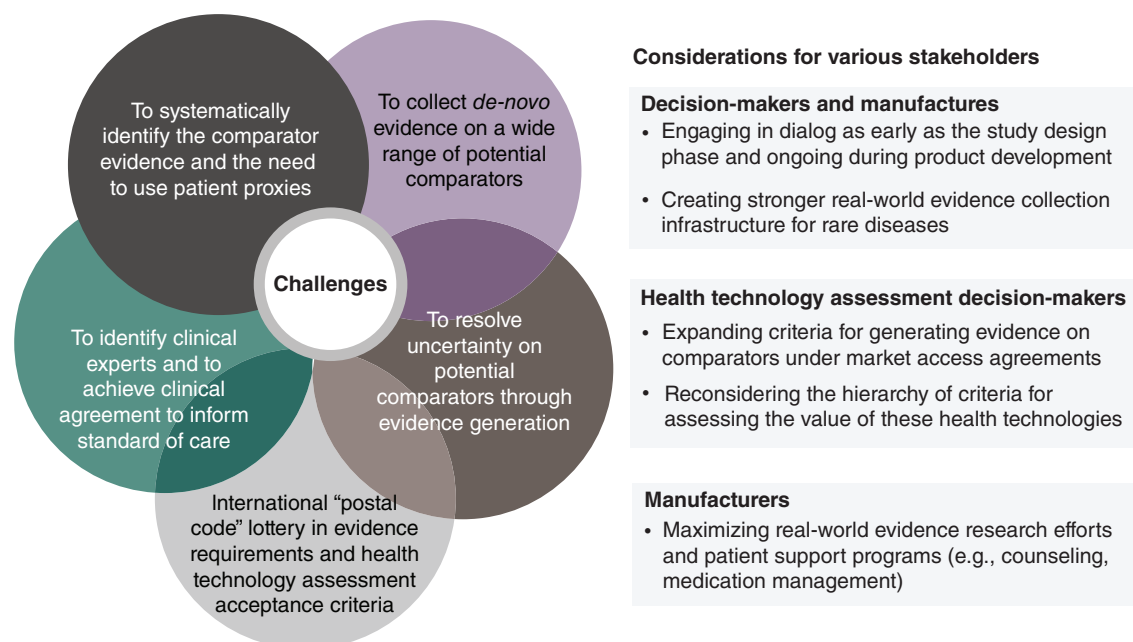


Figure 1. Challenges and HTA considerations for new technologies in indications with no established clinical pathway.

HTA: Health technology assessment.

Difficulties in *de-novo* evidence collection for comparator(s)

De novo primary data gathering may be required to collect information on existing clinical practice (e.g., from patient registries or electronic health records, if available) [37,38], or from prospective studies. However, prospective data collection could be time-consuming, particularly given the small number of patients, and cause delays in patient access to innovative medicines. In addition to the known barriers to the acceptance of real-world evidence (RWE) by HTA bodies (e.g., lack of standardization of data collection, curation procedures, potential biases and limited availability of key confounders, and lack of comparability of the selected external control arm with local or national clinical practice), for rare or very diseases with no standardized clinical pathway, RWE acceptance could be further complicated by the unknown nature of SoC. For these diseases, the number of off-label treatments used in clinical practice may equal the number of patients identified in real-world data. How much uncertainty are decision-makers willing to accept when a wide range of potential (off-label) eligible comparators is considered in the technology assessment, including collapsed treatment classes or a blended comparator? These are some difficult questions but without clear and reproducible HTA criteria, final, acceptance decisions on methodological approaches are taken on a case-by-case basis without sound justification and limiting consistency in decision-making.

The role of clinical experts & patients & challenges in incorporating their input

The role of clinical experts and patients has recently become more important and influential in HTA assessments to support the acceptability of RWE to inform the comparator ‘SoC’ in rare and very rare indications [39]. Recent efforts to standardize the patient and clinical expert elicitation process may increase validity in the data used to estimate comparative clinical and cost-effectiveness for new health technologies targeting a rare or very rare disease without an established SoC [40]. However, there are practical difficulties not only with identifying and recruiting patients and clinical experts, but also with achieving agreement on what may constitute ‘SoC’ across different clinical and geographical settings. For example, in a NICE appraisal [ID3995] on sebelipase alfa, the lack of clinical agreement among the leading medical centers on patients’ management created challenges for the committee to robustly justify the SoC arm in the base-case analysis [41]. Furthermore, generalizability issues when using data from clinical experts across different jurisdictions, although not uncommon in HTAs for rare or very rare diseases, could also pose challenges for its incorporation in decision-making as it may reflect differences in healthcare systems and allocation of local resources [42].

Resolving evidence uncertainty with future evidence generation

Evidence uncertainty is not new for HTA bodies when assessing technologies for rare and very rare diseases [20]. Specialized market access pathways aim to mitigate high levels of uncertainty resulting from limited clinical data (e.g., small sample sizes, lack of control arm in single-arm trials, reliance on surrogate outcomes). However, it is unclear how HTA bodies could handle the uncertainty generated by a lack of data on standardized clinical practice as it is unlikely to be impacted by future evidence generation of the new health technology, even if it becomes available under commercial market arrangements and its reimbursement is linked to future/long-term evidence generation. Potential alternative ways of data generation (i.e., using non-responders from the initial single-arm trial to continue as control arm subjects) may provide some source of comparator evidence, depending on the clinical context.

Fragmented HTA decisions around the world

The lack of standardized evidence requirements in situations where SoC is absent usually results in heterogeneity of coverage decisions across different HTA bodies and limited transparency in decision-making which may imply that different approaches have been used to define SoC in these submissions [43,44]. Fragmented and differentiated implementation of coverage decisions for orphan or ultra orphan drugs is not new; although coverage decisions may be justified in terms of different budget constraints and national health priorities, potential inconsistencies in decision-making across countries in terms of evidence expectations and acceptance thresholds may create an international ‘postal code’ lottery (i.e., variations in healthcare between geographical areas that appear arbitrary and unlinked to health needs) for patient access [45]. This has important implications for issues such as equity and fairness, especially when differences in reimbursement may be perceived as subjective and potentially inconsistent across different rare or very rare disease areas.

This discrepancy can be particularly problematic in imminent EU joint clinical assessments and may pose further operational and financial challenges for manufacturers when planning for evidence generation activities to support submissions to HTA bodies across the globe [34].

Given the challenges outlined above, some evidence and process considerations are proposed herein. They are based on the collective experience of the authors and aim to guide HTA decision-makers, manufacturers, and those involved in technology submissions who want to demonstrate the value of first-in-market therapies for a target population with no established treatment pathway.

HTA evidence generation & process considerations for indications with no established SoC

Early dialog & collaboration between stakeholders & during product development (for both manufacturers & decision-makers)

Early communication between manufacturers, HTA bodies, and patient organizations and patients is crucial [46,47]. This dialog could help clarify the impact of the significant evidence gaps on the natural disease history, standard clinical care, and its impact on comparative effectiveness estimates by acknowledging the potential inability to identify or generate such evidence both pre- and post-HTA submissions. It could also explore alternative trial design considerations for these technologies (e.g., pre- and post-intervention trials) and available evidence packages as well as assess trade-offs in uncertainties generated by different RWE data sources and methodological approaches versus the societal aspects of ensuring access to innovative technologies for patients with rare or very rare diseases. Early collaboration between manufacturers, decision-makers, and other stakeholders can also provide the opportunity to share learnings and encourage dialog across different geographical settings. For example, opportunities for real-world data transferability across borders may be more applicable for these situations, although current related guidance is not comprehensive enough to guide HTA submissions in the near future [42]. Data transferability will help stakeholders to collaborate and understand the evidentiary requirements early in the process and create efficiencies and consistency in decision-making considering the limited treatment options available for patients with these diseases [48]. An example of this collaboration effort is Project HERCULES (Health Research Collaboration United in Leading Evidence Synthesis) led by the Duchenne muscular dystrophy charity in the UK, a ground-breaking initiative that brings together pharmaceutical companies, academics, and industry experts to collaborate on evidence generation activities (e.g., natural disease model, burden-of-illness study, specific health-related quality-of-life tool) that will improve chances of new treatments targeting this rare disease to reach patients faster through HTA routes [49]. Published outputs and access to the data for manufacturers from these collaborations can contribute toward building knowledge sharing on “lessons learned” in previous reviews of HTA decisions for orphan drugs [50].

Furthermore, it is encouraged that these data are made (publicly) available to manufacturers to establish the appropriate comparative clinical and economic value of a new health technology as part of an HTA submission.

Expand criteria for generating evidence on comparators under market access agreements (decision-makers)

As previously noted, clinical management of rare and very rare diseases is often heterogeneous and may involve off-label treatments. In addition, practice can change rapidly when a new treatment option becomes available under market access arrangements or through early patient-access schemes. However, so far, additional evidence generation within market access arrangements is centered around the new technology and not on the clinical practice previously used by the patients. Expansion of market access arrangements on collecting data on previous treatments/comparators may be a potential solution to fill the SoC evidentiary gaps after initial reimbursement linked to future evidence generation (please see example case on nusinersen [NICE technology appraisal 558 [51]]). The application of existing tools and frameworks (i.e., TRUST4RD, NEWDIGS Data Program Framework) can also help manufacturers to both review and prioritize areas of evidence uncertainty with most impact to HTA bodies that can inform early evidence-generation plans [20].

Maximizing RWE research efforts (manufacturers)

HTA bodies are increasingly recognizing the value of observational studies for evidence generation when underpinned by sound methodology and adherence to recent guidelines and methodologically accepted standards [28,52]. Innovative study designs incorporating RWE collection (adaptive study designs, basket trials) or before-and-after study designs focusing on meaningful patient-relevant outcomes may overcome some of the challenges of comparative clinical and economic assessments when there is no established SoC for the targeted condition [53,54]. Existing frameworks such as the use of a meaningful, valid, expedited, and transparent evidence framework [55], the US FDA's Sentinel Initiative [56], and value-based frameworks specific for rare and very rare diseases [57], as well as existing analytical methodologies proposed by international initiatives (such as GetReal), can guide some of the decisions on evaluating clinical estimates between the new technology under assessment and what patients most likely would have experienced in clinical practice if there was SoC (i.e., using weighting approaches) [58].

Creating stronger RWE collection infrastructure for rare & very rare diseases & common data models (all stakeholders)

The creation of RWE repositories for rare and very rare diseases, especially through data collected from electronic health records and patient registries, and the integration of RWE into clinical programs may be fragmented and complex to implement [59]. However, it would facilitate the appraisal of technologies that are first-in-market for rare diseases with high unmet needs. Several ongoing efforts at national and international levels such as the European Partnership under Horizon Europe Rare Diseases [60] will provide the context to further standardize data collection processes (including common data elements) for these diseases [61,62,63]. The Critical Path Institute's Rare Disease Cures Accelerator Data Analytics Platform [64] (supported by the US FDA and the National Organization for Rare Disorders) and RARE-X [65] also represent innovative platforms focused on aggregating, curating, and integrating datasets to improve the rare disease research and development ecosystem that can provide granulated data for supporting different HTA submissions. Overcoming data access barriers is a critical requirement for these opportunities to be fully utilized by manufacturers.

Conclusion

Generating evidence on comparators for new technologies targeting rare or very rare conditions with no established clinical care is challenging and threatens timely patient access to innovative technologies. Strong early collaborations between manufacturers and HTA decision-makers will provide the platform to maximize the potential of RWE to fill the evidentiary gaps for the 'unknown' SoC and provide transparency for manufacturers regarding decision criteria, acceptable methodologies and RWE collection efforts.

Summary points

- The identification of a comparator 'standard of care' ('SoC') arm against which to assess the added benefit of new technologies for rare and very rare diseases is a significant challenge in health technology assessment (HTA) submissions when there is no established treatment pathway. This compounds other common evidence generation challenges in these diseases.
- HTA bodies have indicated that they are moving toward greater flexibility in understanding and responding to these challenges; this includes weighing a broader notion of value for these technologies (e.g., severity of disease, equity), considering market access agreements (e.g., managed entry agreements, patient access schemes, coverage with evidence development, risk-sharing arrangements, and performance-based agreements), and allowing for higher levels of uncertainty in clinical estimates and economic modelling when evidence generation and generalizability of a comparator SoC may be beyond the control of manufacturers.
- However, a lack of concrete guidance on the topic, including explicit HTA acceptance of methodological approaches to overcome the challenges presented in this commentary (e.g., adaptive study designs, use of proxy populations in systematic reviews, expanding evidence generation on comparators as part of market access arrangements), may create inconsistency in decision-making, contribute to low evidentiary standards in manufacturers submissions and restrict the full potential of innovative treatments to benefit patients.
- Learnings from case studies using previous HTA submissions (both with positive and negative outcomes) by creating living (regularly updated) data platforms (e.g., similarly to surrogate endpoint tables by the FDA [66]) could form the foundation for setting up clear and methodologically based standards in this area. As more HTA submissions become available in rare and very rare indications, these standards could be updated, and case studies could be used as precedents.
- However, alignment of the standards across HTAs from different jurisdictions, and even between regulatory and HTA bodies, would still be needed to address the challenges outlined above and help accelerate patient access to innovative medicines across the globe.
- Furthermore, recent developments to initiate joint clinical assessments of new technologies across countries in the European Union will further highlight the need to establish SoC for rare and very rare diseases across Europe.
- Additional flexibility in evidence generation for manufacturers would also help facilitate the aim of policy-makers to provide more equitable treatment for patients with rare or very rare diseases [67]. Several examples include the use of existing infrastructure for rare disease registries (e.g., European Rare Disease Registry Infrastructure [68]) and early planning of patient registries for rare or very rare populations. The expansion of these incentives could also ultimately encourage manufacturers to support research and development for these less profitable technologies in disease areas with no established SoC [67,69,70].

Author contributions

The authors declare that this is an original work. All authors contributed equally.

Acknowledgments

The authors thank Colleen Dumont for writing and editorial support of this manuscript. The views and opinions expressed here are those of the authors; they do not reflect the opinions of their organizations.

Financial disclosure

The authors have no financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Competing interests disclosure

G Sarri and M Rizzo are employees of Cytel, Inc. V Federico Paly and L Hernandez are employees of Takeda Pharmaceuticals America, Inc. S Upadhyaya was employed by the National Institute for Health and Care Excellence when this manuscript was drafted. The authors have no other competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing disclosure

Editorial assistance for this manuscript was funded by Takeda Pharmaceuticals America, Inc.

Open access

This work is licensed under the Attribution-NonCommercial-NoDerivatives 4.0 Unported License. To view a copy of this license, visit <https://creativecommons.org/licenses/by-nc-nd/4.0/>

References

1. United States Food and Drug Administration. Orphan Drug Act – Relevant Excerpts. (2013). <https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/orphan-drug-act-relevant-excerpts>
2. European Medicines Agency. Orphan designation: overview. (2022). <https://www.ema.europa.eu/en/human-regulatory/overview/orphan-designation-overview>
3. Gov.uk. UK Rare Diseases Framework. (2021). <https://www.gov.uk/government/publications/uk-rare-diseases-framework>
4. National Institute for Health and Care Research. Themed call: very rare diseases. (2012). <https://www.nihr.ac.uk/documents/themed-call-very-rare-diseases-2012/24064>
5. Schlender M, Adarkwah CC, Gandjour A. Budget impact analysis of drugs for ultra-orphan non-oncological diseases in Europe. *Expert Rev. Pharmacoecon. Outcomes Res.* 15(1), 171–179 (2015).
6. Impact HTA. Work Package 10: Country Vignettes. (2022). <https://www.impact-hta.eu/country-vignettes>
7. Nicod E, Whittall A, Drummond M, Facey K. Are supplemental appraisal/reimbursement processes needed for rare disease treatments? An international comparison of country approaches. *Orphanet J. Rare Dis.* 15(1), 189 (2020).
8. Scottish Medicines Consortium. Search results. (2022). <https://www.scottishmedicines.org.uk/search/?keywords=guidance+on+npaf>
9. EUR-Lex (Access to European Union law). Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. (2019). <http://data.europa.eu/eli/reg/2000/141/oj/eng>
10. Nicod E, Annemans L, Bucsics A, Lee A, Upadhyaya S, Facey K. HTA programme response to the challenges of dealing with orphan medicinal products: process evaluation in selected European countries. *Health Policy.* 123(2), 140–151 (2019).
11. Slade A, Isa F, Kyte D *et al.* Patient reported outcome measures in rare diseases: a narrative review. *Orphanet J. Rare Dis.* 13(1), 61 (2018).
12. Kakkis ED, O'Donovan M, Cox G *et al.* Recommendations for the development of rare disease drugs using the accelerated approval pathway and for qualifying biomarkers as primary endpoints. *Orphanet J. Rare Dis.* 10, 16 (2015).
13. Hughes-Wilson W, Palma A, Schuurman A, Simoens S. Paying for the Orphan Drug System: break or bend? Is it time for a new evaluation system for payers in Europe to take account of new rare disease treatments? *Orphanet J. Rare Dis.* 7, 74 (2012).
14. Wagner M, Khoury H, Willet J, Rindress D, Goetghebuer M. Can the EVIDEM Framework tackle issues raised by evaluating treatments for rare diseases: analysis of issues and policies, and context-specific adaptation. *Pharmacoeconomics* 34(3), 285–301 (2016).
15. Morel T, Arickx F, Befrits G *et al.* Reconciling uncertainty of costs and outcomes with the need for access to orphan medicinal products: a comparative study of managed entry agreements across seven European countries. *Orphanet J. Rare Dis.* 8, 198 (2013).
16. Stafinski T, Glennie J, Young A, Menon D. HTA decision-making for drugs for rare diseases: comparison of processes across countries. *Orphanet J. Rare Dis.* 17(1), 258 (2022).
17. National Institute for Health and Care Excellence. Changes we're making to health technology evaluation. (2022). <https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/changes-to-health-technology-evaluation>
18. Scottish Medicines Consortium. Updated new product assessment form. (2017). <https://www.scottishmedicines.org.uk/about-us/latest-update/updated-new-product-assessment-form/>
19. Institute for Clinical and Economic Review. Value Assessment Framework. (2022). <https://icer.org/our-approach/methods-process/value-assessment-framework/>
20. Annemans L, Makady A. TRUST4RD: tool for reducing uncertainties in the evidence generation for specialised treatments for rare diseases. *Orphanet J. Rare Dis.* 15(1), 127 (2020).
21. Zhou N, Ji H, Li Z *et al.* Influencing factors of health technology assessment to orphan drugs: empirical evidence in England, Scotland, Canada, and Australia. *Front. Public Health.* 10, 861067 (2022).
22. Danzon PM. Affordability challenges to value-based pricing: mass diseases, orphan diseases, and cures. *Value Health.* 21(3), 252–257 (2018).
23. Brenna E, Polistena B, Spandonaro F. The implementation of health technology assessment principles in public decisions concerning orphan drugs. *Eur. J. Clin. Pharmacol.* 76(6), 755–764 (2020).
24. Institute for Clinical and Economic Review. The Next Generation of Rare Disease Drug Policy: Ensuring Both Innovation and Affordability. (2022). https://icer.org/wp-content/uploads/2022/04/ICER-White-Paper-The-Next-Generation-of-Rare-Disease-Drug-Policy_040722.pdf
25. United States Food and Drug Administration. Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products. (2023). <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-design-and-conduct-externally-controlled-trials-drug-and-biological-products>

26. European Medicines Agency. Single-arm trials as pivotal evidence for the authorisation of medicines in the EU. (2023). <https://www.ema.europa.eu/en/news/single-arm-trials-pivotal-evidence-authorisation-medicines-eu>
27. National Institute for Health and Care Excellence. Real-world evidence framework. (2022). <https://www.nice.org.uk/about/what-we-do/real-world-evidence-framework>
28. Canadian Agency for Drugs and Technologies in Health. Guidance for Reporting Real-World Evidence. (2023). <https://www.cadth.ca/guidance-reporting-real-world-evidence>
29. Vanier A, Fernandez J, Kelley S *et al*. Rapid access to innovative medicinal products while ensuring relevant health technology assessment. Position of the French National Authority for Health. *BMJ Evidence Based Med*. bmjebm-2022-112091 (2023).
30. Fung A, Yue X, Wigle PR, Guo JJ. Off-label medication use in rare pediatric diseases in the United States. *Intractable Rare Dis. Res.* 10(4), 238–245 (2021).
31. Olivier T, Prasad V. Amivantamab and mobocertinib in exon 20 insertions EGFR mutant lung cancer, challenge to the current guidelines. *Transl. Oncol.* 23, 101475 (2022).
32. Nestler-Parr S, Korchagina D, Toumi M *et al*. Challenges in research and health technology assessment of rare disease technologies: report of the ISPOR Rare Disease Special Interest Group. *Value Health.* 21(5), 493–500 (2018).
33. Davis C, Naci H, Gурinar E, Poplavska E, Pinto A, Aggarwal A. Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: retrospective cohort study of drug approvals 2009–13. *BMJ.* 359, j4530 (2017).
34. The Professional Society for Health Economics and Outcomes Research. Routing RWE Sources in HTA Submissions When Standard of Care Is Not Established: How to Robustly Validate Your Uncertainties. (2023). <https://www.ispor.org/conferences-education/conference/s/upcoming-conferences/ispor-2023/program/program/session/intl2023-3639/15711>
35. Clarke S, Ellis M, Brownrigg J. The impact of rarity in NICE's health technology appraisals. *Orphanet J. Rare Dis.* 16(1), 218 (2021).
36. Leadley R, de Kock S, Lang S, Kleijnen J. Challenges of conducting a systematic review on the prevalence of rare diseases (Poster abstract for Cape Town Global Evidence Summit). (2017). <https://abstracts.cochrane.org/2017-global-evidence-summit/challenges-conducting-systematic-review-prevalence-rare-diseases>
37. United States Food and Drug Administration. GUIDANCE DOCUMENT: Rare Diseases: Natural History Studies for Drug Development. (2019). <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rare-diseases-natural-history-studies-drug-development>
38. United States Food and Drug Administration. FDA Approves First COVID-19 Vaccine. <https://www.fda.gov/news-events/press-announcements/fda-approves-first-covid-19-vaccine2021>
39. National Institute for Health and Care Excellence. Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation [TA429]. (2017). <https://www.nice.org.uk/guidance/ta429>
40. The Professional Society for Health Economics and Outcomes Research. Structured Expert Elicitation for Healthcare Decision Making. (2022). <https://www.ispor.org/member-groups/task-forces/structured-expert-elicitation-for-healthcare-decision-making>
41. National Institute for Health and Care Excellence. Sebelipase alfa for treating Wolman disease [ID3995]; In development [GID-HST10047] Expected publication date: 10 January 2024. (2024). <https://www.nice.org.uk/guidance/indevelopment/gid-hst10047>
42. Jaksa A, Arena PJ, Chan KKW, Ben-Joseph RH, Jónsson P, Campbell UB. Transferability of real-world data across borders for regulatory and health technology assessment decision-making. *Front. Med.* 9, 1073678 (2022).
43. Hogervorst MA, Vreman RA, Mantel-Teeuwisse AK, Goetsch WG. Reported challenges in health technology assessment of complex health technologies. *Value Health.* 25(6), 992–1001 (2022).
44. Blonda A, Barcina Lacosta T, Toumi M, Simoens S. Assessing the value of nusinersen for spinal muscular atrophy: a comparative analysis of reimbursement submission and appraisal in European countries. *Front. Pharmacol.* 12, 750742 (2021).
45. Roscamp JA, D'Cruz DP. The funding lottery for potentially life-threatening rare diseases. *Rheumatology (Oxford)*. 57(1), 1–2 (2018).
46. European Medicines Agency. PRIME: priority medicines. (2022). <https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines>
47. Gov.uk. Guidance: Innovative Licensing and Access Pathway. (2022). <https://www.gov.uk/guidance/innovative-licensing-and-access-pathway>
48. Trowman R, Powers A, Ollendorf DA. Considering and communicating uncertainty in health technology assessment. *Int. J. Technol. Assess. Health Care.* 37(1), e74 (2021).
49. Duchenne UK. Accelerating access to treatments. (2023). <https://www.duchenneuk.org/accelerating-access-to-treatments/>
50. Adkins EM, Nicholson L, Floyd D, Ratcliffe M, Chevrou-Severac H. Oncology drugs for orphan indications: how are HTA processes evolving for this specific drug category? *Clinicoecon. Outcomes Res.* 9, 327–342 (2017).
51. National Institute for Health and Care Excellence. Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease [TA558]. (2019). <https://www.nice.org.uk/guidance/ta558>
52. National Institute for Health and Care Excellence. NICE real-world evidence framework: corporate document [ECD9]. (2022). <https://www.nice.org.uk/corporate/ecd9/chapter/overview>

53. Varnai P, Dave A, Farla K, Nooijen A, Petrosova L. The Evidence REVEAL Study: Exploring the Use of Real-World Evidence and Complex Clinical Trial Design by the European Pharmaceutical Industry. *Clin. Pharmacol. Ther.* 110(5), 1180–1189 (2021).
54. Xia AD, Schaefer CP, Szende A, Jahn E, Hirst MJ. RWE framework: an interactive visual tool to support a real-world evidence study design. *Drugs Real World Outcomes.* 6(4), 193–203 (2019).
55. Gatto NM, Reynolds RF, Campbell UB. A structured preapproval and postapproval comparative study design framework to generate valid and transparent real-world evidence for regulatory decisions. *Clin. Pharmacol. Ther.* 106(1), 103–115 (2019).
56. United States Food and Drug Administration. FDA's Sentinel Initiative. (2023). <https://www.fda.gov/safety/fdas-sentinel-initiative>
57. McQueen RB, Mendola ND, Jakab I, Bennett J, Nair KV, Németh B *et al.* Framework for Patient Experience Value Elements in Rare Disease: A Case Study Demonstrating the Applicability of Combined Qualitative and Quantitative Methods. *Pharmacoecon. Open.* 7(2), 217–228 (2023).
58. Blonda A, Denier Y, Huys I, Simoens S. How to Value Orphan Drugs? A Review of European Value Assessment Frameworks. *Front. Pharmacol.* 12 (2021).
59. European Commission. Rare Disease Day: a new EU platform to support better diagnosis and treatment. (2019). https://ec.europa.eu/commission/presscorner/detail/en/IP_19_1414.
60. Abaza H, Kadioglu D, Martin S *et al.* Domain-specific common data elements for rare disease registration: conceptual approach of a European joint initiative toward semantic interoperability in rare disease research. *JMIR Med. Inform.* 10(5), e32158 (2022).
61. European Commission. European Platform on Rare Disease Registration (EU RD Platform). (2022). <https://eu-rd-platform.jrc.ec.europa.eu/en>
62. Jørgensen J, Mungapen L, Kefalas P. Data collection infrastructure for patient outcomes in the UK – opportunities and challenges for cell and gene therapies launching. *J. Market Access Health Pol.* 7(1), 1573164 (2019).
63. Montilla S, Xoxi E, Russo P, Cicchetti A, Pani L. Monitoring Registries at Italian Medicines Agency: Fostering Access, Guaranteeing Sustainability. *Int. J. Technol. Assess. Health Care.* 31(4), 210–213 (2015).
64. Critical Path Institute. Home page. (2023). <https://c-path.org/programs/rdca-dap/overview/resources/>
65. RARE-X. Home page. (2023). <https://rare-x.org/>
66. United States Food and Drug Administration. Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure. (2022). <https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure>
67. Aartsma-Rus A, Doms M, Le Cam Y. Orphan medicine incentives: how to address the unmet needs of rare disease patients by optimizing the European Orphan Medicinal Product Landscape Guiding Principles and Policy Proposals by the European Expert Group for Orphan Drug Incentives (OD Expert Group). *Front. Pharmacol.* 12, 744532 (2021).
68. European Commission. European Rare Disease Registry Infrastructure (ERDRI). (2023). https://eu-rd-platform.jrc.ec.europa.eu/erdri-description_en
69. United States Food and Drug Administration. Medical products for rare diseases and conditions. (2022). <https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions>
70. European Medicines Agency. Orphan incentives. (2023). <https://www.ema.europa.eu/en/human-regulatory/research-development/orphan-designation/orphan-incentives>