Evidence Generation Planning for and Economic Modeling of Rare Progressive Pediatric Diseases: Challenges and Prospective Solutions

EE531

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Background

- The majority of rare diseases are genetic, and half of them affect children.[1,2] Many are progressive multi-system conditions for which novel disease-modifying treatment options are under development,[3-5] encouraged by public health initiatives and global regulatory changes supporting drug development for rare diseases.[6-8]
- Demonstrating value is particularly important to maximize treatment access, but challenges are especially apparent in rare diseases with no or few current options available.[6,9-11]

Objective

- This study reviews common barriers to constructing and informing health economic models for rare progressive pediatric diseases and explores potential solutions.

Methods

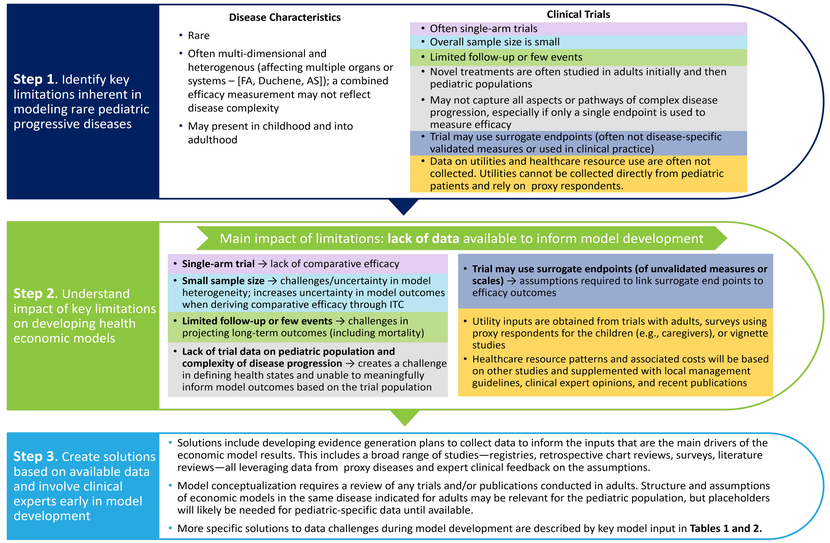
- Economic models developed for a series of rare progressive diseases in pediatric populations were reviewed and evaluated against ISPOR criteria and AdVISHE guidelines.[12,13]
- The review highlighted and itemized challenges that were encountered in conducting health economic assessments associated with novel interventions for these conditions in children. These challenges directly impact the conceptualization of an appropriate model structure as well as impact the data available to inform model inputs, including the following:
  - *Population and clinical outcomes*: Baseline patient characteristics, mortality, projection of long-term outcomes
  - *Treatment*: Relative efficacy of treatments over time
  - *Cost*: Resource use and costs accrued at events (e.g., adverse events, monitoring, disease management) with and without treatment
  - *Utility*: Quality of life associated with events for patients receiving or not receiving treatment
- The study also summarized the impact of these challenges as well as common approaches to resolve them that align with best practices. These findings may be considered in future health economic model development for rare progressive pediatric diseases.

Conclusions

- While data available in the literature are limited to guide model development, natural history studies, data from registries, or proxy diseases may be used along with consultation with clinicians and key stakeholders to better understand rare pediatric progressive diseases and inform model inputs.
- Therefore, anticipating evidence generation and economic modeling challenges early in orphan drug development for rare progressive diseases can help guide conceptualization and development of health economic analyses that align with current guidelines and best practices and accelerate access to novel therapeutics in pediatric populations.

Results

Figure 1. Challenges, Impacts, and Key Solutions of Modeling Rare Pediatric Progressive Diseases



Abbreviations: AS = Alport syndrome; FA = Friedreich's ataxia; ITC = indirect treatment comparison; QoL = quality of life.

- Health economic models were reviewed in eight rare diseases, metachromatic leukodystrophy, Duchenne muscular dystrophy, Pompe disease, Gaucher disease, Alport syndrome, Friedreich's ataxia, cystic fibrosis, and acid sphingomyelinase deficiency disease.[14-26]
- Pediatric clinical trials for rare diseases frequently have heterogenous populations, small sample sizes, single-arm design, and brief follow-up, which lead to data gaps and limited data inputs necessary for model development. In addition, model conceptualization is frequently challenged by a paucity of published literature to define the natural history of a disease in the appropriate patient population, especially in children. A summary of the data challenges and impacts observed during model development are illustrated in **Figure 1**.
- To overcome data gaps, economic analyses exploited natural history studies and data from regional/global registries. In addition, identifying a well-studied proxy disease was broadly necessary for conceptualization, informing model inputs, and supporting cross-validation.
- Consistent with ISPOR and AdVISHE guidelines,[12,13] clinicians and key stakeholders were commonly consulted to define/confirm populations of interest, characterize the standard of care, and develop a better understanding of the condition. Thorough sensitivity analyses were essential to assess the implications of potential parameter biases and structural uncertainty, in accordance with guidelines.

Table 1. Summary of Solutions: Relative Efficacy, Long-term Outcomes, and Mortality

Consideration	Solutions	References
Population	• Model conceptualization requires a review of trials and publications conducted in adults. Patient-level data from registries may also be evaluated to determine key patient characteristics that affect disease progression. Structure and assumptions of economic models in the same disease indicated for adults may be relevant for the pediatric population.	25,26
Lack of comparative data	• Registries or chart reviews may be used to derive relative efficacy estimates. Access to the existing registry data or chart reviews may require collaboration with academic institutions. Collaboration should be established ahead of time. Model can be built with flexibility to allow for data to be used from future studies.	
Uncertainty in long-term model outcomes	• Use data from various sources including clinical trials, natural history studies, or registry studies. • Consult expert clinicians to confirm assumptions and long-term extrapolations of the outcomes. • When a rare disease is well studied, model validation is feasible. The ability of the model projections and alignment with real-world survival data can be assessed. When less well studied, or current management has evolved over time and improved outcomes, there may be limited evidence to inform or collaborate the model. In some instances formal methods to elicit expert opinion (e.g., SHELF) and inform some inputs are used. • Range of scenario analyses can be performed to test modeling assumptions and their impact on the results.	14-22,24
Mortality	• When a small number of deaths are reported in a trial, typical approaches used to estimate mortality such as parametric survival analyses cannot be conducted. • Use published mortality data or individual patient-level data from a natural history study or registry data to create or estimate survival curves. • Calibrate an overall survival curve for the general population using an SMR to match the overall survival expected for patients with a specific disease. • Leverage mortality estimates in comparable health states for other diseases.	14,16-18,20,22,24
Time on treatment	• Include approach for handling treatment discontinuation as well as how treatment efficacy will be impacted by discontinuation using assumptions with input from expert clinicians. • Assumptions to be tested in sensitivity analyses.	21
Capture multiple endpoints	• Consider multiple efficacy endpoints from the trial where available when defining disease states or milestones that will capture important QoL or cost benefit from receiving the treatment. • Test uncertainty/assumptions in sensitivity analyses.	16,25,26
Heterogeneity in population and outcomes	• To account for heterogeneity, one option is to use subgroups, which can be followed in multi-cohort modeling. For example, a CEM could aim to include flexibility for an overall population analysis that weights the outcomes of several subgroups. A model with these subgroups would typically aim to be homogenous, with relevant sources for the differing clinical input values. If subgroup analyses lead to oversimplification of the disease course, then an individual patient simulation is considered. • However, there may be a lack of data available to inform these subgroups due to a small patient population in the trial. Some inputs (i.e., progression modifiers) may need to be assumed equal to observed data from a natural history cohort. Assumptions will likely be needed and confirmed with an expert clinician, or data from a proxy disease may be used.	14,16-18,23,26

Abbreviations: CEM = cost-effectiveness model; SMR = standardized mortality ratio; QoL = quality of life.

Table 2. Summary of Solutions: Utility, Costs, and Resource Use

Challenges	Solutions	References
Lack of data available to inform utilities/resource use in model (i.e., data not collected in trial, paucity of data from literature/registries)	• Utilities: Leverage utility data collected from adults and proxy respondents for the children and plan to conduct vignette studies aligned with the health states. • Resource use/Costs: Perform retrospective data analyses when available. • Possibly use published studies in same or proxy diseases; however, relying on analogue diseases may not always be acceptable to HTAs. • Consult a clinician to confirm the appropriateness of using data from analog diseases to inform some health state inputs. • Test uncertainty/assumptions in sensitivity analyses.	14-18,20-23
Caregiver disutilities not considered by all HTAs	• Consider including caregiver burden in model in appropriate settings, for very severe diseases it is possible to assume more than one caregiver. This should be confirmed with input from expert clinicians. • Test uncertainty in sensitivity analyses.	
Caregiver costs	Conduct caregiver surveys and studies: • The human capital approach is used by some HTAs to derive the indirect costs due to productivity losses associated with paid employment of caregivers. This considers the working population and not "unpaid productivity loss," which is what often impacts many of these caregivers. • Use the "proxy good" approach, which provides insight into the cost of replacing informal (unpaid) care with formal paid care. • Informal (unpaid) hours can be valued by applying proxy hourly wages for formal care (paid) substitutes (e.g., personal care aides). • A simpler alternative is estimation of "opportunity costs" where the wage rates are based on the caregiver age and income or the population wage. • Test uncertainty in sensitivity analyses.	27

Abbreviations: HTA = health technology assessment; TTO = time trade-off.

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