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Economic Modeling Considerations for Rare Diseases

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ABSTRACT

Objectives: To identify challenges that affect the feasibility and rigor of economic models in rare diseases and strategies that manufacturers have employed in health technology assessment submissions to demonstrate the value of new orphan products that have limited study data. **Methods:** Targeted reviews of PubMed, the National Institute for Health and Care Excellence's (NICE's) Highly Specialised Technologies (HST), and the Scottish Medicines Consortium's (SMC's) ultra-orphan submissions were performed. **Results:** A total of 19 PubMed studies, 3 published NICE HSTs, and 11 ultra-orphan SMC submissions were eligible for inclusion. In rare diseases, a number of different factors may affect the model's ability to comply with good practice recommendations. Many products for the treatment of rare diseases have an incomplete efficacy and safety profile at product launch. In addition, there is often limited available natural history and epidemiology data. Information on the direct and indirect cost burden of an orphan disease also may be limited, making it difficult to estimate the potential economic benefit of treatment. These challenges can prevent accurate estimation of a new product's benefits in relation to costs. Approaches that can address such challenges include using patient and/or clinician feedback to inform model assumptions; data from disease analogues; epidemiological techniques, such as matching-adjusted indirect comparison; and long-term data collection. **Conclusions:** Modeling in rare diseases is often challenging; however, a number of approaches are available to support the development of model structures and the collation of input parameters and to manage uncertainty.

Keywords: costs and cost analysis, economic, economics, medical, models, rare diseases.

Introduction

The definitions used for orphan or rare diseases, that is, medical conditions with low prevalence, are often inconsistent from country to country. In the United States, the Food and Drug Administration defines a rare disease as one that affects fewer than 200,000 individuals [1]. The European Commission defines an orphan disease as that which affects fewer than 5 people per 10,000, or approximately 246,000 individuals in the European Union [2]. This same body defines ultra-orphan diseases as those affecting fewer than 1 person in 50,000 in the European Union [3].

Products developed to treat orphan diseases may have high drug acquisition costs, owing to large research and development expenditures and postmarketing surveillance program outlays with corresponding low patient volumes. Because of this, regulatory authorities have introduced incentives to encourage the development of orphan products. In the United States, the 1983 Orphan Drug Act allows for a 7-year period of market exclusivity after the launch of an orphan drug treatment, along with corporate tax incentives [1]. In the European Union, products granted orphan designation are eligible for 10 years of market exclusivity and protocol assistance at a reduced charge [4].

Despite incentives and favorable tax treatments, orphan drug products must undergo formal health technology assessment (HTA) economic evaluation after regulatory approval, to gain reimbursement in some (but not all) European countries, and most orphan medicines are not found to be cost effective when measured by standard thresholds [5]. Furthermore, there may be challenges in developing evaluations of sufficient methodological quality and certainty to meet HTA requirements [6,7].

A number of countries have specialized agency reviewers for rare diseases, thus ensuring that factors other than cost-effectiveness are considered during the appraisal process. The Australian Life Saving Drugs Program aims to provide subsidized access to expensive yet potentially life-saving drugs for very rare life-threatening conditions [8]. One of the many criteria for funding by this program is that a drug must be accepted as clinically effective yet be denied listing on the Pharmaceutical Benefits Scheme because of its failure to meet required cost-effectiveness criteria.

In the United Kingdom, the National Institute for Health and Care Excellence's (NICE's) Highly Specialised Technologies (HST) program considers drugs for very rare conditions and provides recommendations on the use of new and existing highly specialized medicines and treatments within the National Health Service (NHS) [9]. As part of the HST review process, a number of criteria are considered, including the nature of the condition, the impact of the new technology, the cost to the NHS and

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Table 1 – Targeted literature search of the PubMed database (performed February 28, 2017).

Term group	Search number	Search terms	No. of PubMed hits
Treatment	1	"Orphan Drug Production" [MeSH] OR "orphan drug" [Text Word] OR "orphan drugs" [Text Word] OR "orphan medicine" [Text Word] OR "orphan medicines" [Text Word] OR "ultra-orphan drug" [Text Word] OR "ultra-orphan drugs" [Text Word] OR "orphan product" [Text Word] OR "orphan products" [Text Word] OR "ultra-orphan product" [Text Word] OR "ultra-orphan products" [Text Word] OR (("rare disease" [Text Word] OR "rare diseases" [Text Word] OR "ultra-rare disease" [Text Word] OR "ultra-rare diseases" [Text Word]) AND (treat* [Text Word] OR therap* [Text Word] OR medicine* [Text Word]))	15,602
Economic models	2	#1 AND ("Cost-Benefit Analysis" [MeSH] OR "Models, Economic" [MeSH] OR "Models, Econometric" [MeSH] OR "Costs and Cost Analysis" [MeSH] OR "Economics" [MeSH] OR "Economics, Hospital" [MeSH] OR "Economics, Medical" [MeSH] OR "Economics, Nursing" [MeSH] OR "Economics, Pharmaceutical" [MeSH] OR "Cost Savings" [MeSH] OR cost effective* [Text Word] OR cost-effective* [Text Word] OR modeling [Text Word] OR modelling[Text Word] OR economic model* [Text Word] OR {model* [Text Word] AND (cost [Text Word] OR costs [Text Word] OR economic* [Text Word] OR pharmacoeconomic* [Text Word])} OR Markov [Text Word] OR "decision analysis" [Text Word] OR "decision-analytic models" [Text Word] OR "cost consequence" [Text Word] OR [(cost[Text Word] OR costs [Text Word]) AND (effective* [Text Word] OR utilit* [Text Word] OR benefit*[Text Word] OR minimi* [Text Word])} OR "discrete event simulation" [Text Word] OR "cost analysis" [Text Word] OR "cost-analysis" [Text Word] OR "cost-minimisation analysis" [Text Word] OR economic benefit* [Text Word] OR "cost utility" [Text Word] OR "cost-utility" [Text Word] OR costminimization [Text Word] OR costminimisation [Text Word] OR "cost-minimization" [Text Word] OR "cost-minimisation" [Text Word] OR "cost minimization" [Text Word] OR "cost minimisation" [Text Word] OR "budget impact" [Text Word] OR econometric [Text Word] OR "economic evaluation" [Text Word])	788
Exclusions	3	"Animals" [MeSH] NOT "Humans" [MeSH]	4,301,964
	4	"Comment" [Publication Type] OR "Letter" [Publication Type]	1,238,672
Totals	5	#2 NOT (#3 OR #4)	750
	6	Publication date from 2007/01/01 to 2017/02/28	556

MeSH, medical subject heading.

Personal Social Services, the technology's value for money, and the impact of the technology beyond direct health benefits. NICE has recently announced a new approach regarding how treatments for very rare conditions are evaluated in the HST program. Specifically, treatments shown to provide significant quality-adjusted life-year (QALY) benefits are assessed against a higher maximum threshold of £300,000 per QALY gained [10]. This new approach of including a threshold for treatments assessed via the HST route may not be seen as progressive, as some may argue it introduces less flexibility for NICE in their decision process.

In addition, the Scottish Medicines Consortium (SMC) and All Wales Medicines Strategy Group have revised their processes for appraising drugs for very rare conditions and now allow increased involvement from patients and clinicians [11,12]. However, not all HTA organizations have a separate process for evaluating rare diseases. Canada, for example, uses the same criteria to appraise drugs for rare diseases as are used for common diseases [13].

The aim of this article is to identify the challenges facing economic modeling in rare diseases and to highlight how manufacturers have demonstrated the value of orphan products that have limited study data.

Methods

A targeted electronic search of the PubMed database was performed to identify the challenges that will affect economic modeling in rare diseases. The search strategy is presented in Table 1. Economic publications presenting limitations associated with modeling in rare diseases and/or strategies to address these limitations were identified. Titles and abstracts (level 1 screen) and full-text publications (level 2 screen) were reviewed by one reviewer.

The targeted PubMed review was supplemented with a targeted review of NICE's HST and SMC's ultra-orphan appraisals, to identify the specific limitations of appraised orphan products. To restrict the scope of the review, a targeted review of NICE HST submissions published before October 13, 2016 and of SMC ultra-orphan appraisals published between October 13, 2015 and October 13, 2016 was used to identify strategies that manufacturers have employed to demonstrate the value of orphan products that have limited study data. NICE HST and SMC ultra-orphan HTA submissions were screened for eligibility by one reviewer.

Results

Targeted Review of Challenges That Affect Modeling in Rare Diseases

The targeted literature search identified 556 titles and abstracts. Following the level 1 screen, 50 full-text publications were eligible for the level 2 screen. Of these, 19 publications presented relevant information on the challenges that affected rare disease models. The results of the targeted literature review are presented in Table 2. A summary of the challenges identified by the targeted

Table 2 – PubMed targeted literature review results.

Search results	Number of articles identified
Records identified through PubMed database searches and entering level 1 screening (titles and abstracts)	556
Studies entering level 2 screening (full-text publications)	50
Studies presenting challenges and/or information on modeling in rare diseases	19

literature review is presented in Table 3. These challenges relate to limitations in the clinical and economic evidence. In addition, the available data registries that may help address these clinical and economic data limitations are associated with their own limitations that can affect the quality of the available evidence base.

Development of economic evaluations for orphan products is often inhibited by limited or weak clinical and safety data at product launch [5]. The results of the targeted literature review highlighted that the use of randomized, controlled trials, considered the gold standard in study design for establishing clinical efficacy [14], is often precluded because of the small size of orphan disease populations worldwide. In addition, a number of challenges were identified that might contribute to uncertainty in the clinical data and, ultimately, the results of an economic model. These challenges include inadequately powered trials [15,16]; heterogeneity in the trial population, subgroups, and endpoints that prevent the potential use of network meta-analyses to support economic model development [15,17,18]; the use of surrogate end points or biomarkers rather than "hard" clinical outcomes that may be of more relevance to payers [19,20]; and the limited number of validated instruments to assess severity and progression of the rare disease [16,21].

In addition, clinical trials in rare diseases may not include a control arm, because of ethical concerns, and there may be limited effective comparators and comparator data [17,20,22], all of which challenge the development of comparative economic evidence. Furthermore, many orphan diseases are pediatric and/or may be associated with increased mortality rates [23], and there may be additional ethical considerations in such trials' designs, particularly in placebo-controlled clinical trials.

The targeted literature review also emphasized that trials in rare diseases may be stopped early on ethical grounds [24] or could have a prospectively planned short duration [17,19]. Because orphan diseases are often slowly progressive and chronic, clinical evidence derived from trials with short durations can result in uncertainty when a model is developed using a lifetime time horizon. Stopping a trial early can be used to potentially expedited publication of results and ultimately approval of the drug; however, stopping a trial early may prevent sufficient safety data from being collated [25].

Another challenge identified by the targeted review was that there may be a limited understanding of the rare disease's natural history with which to inform trial design [16,24,26]. This challenge also is relevant to developing the health states for an economic model.

When there are limited or uncertain clinical data available to support the development of an economic model, health economists may turn to other clinical data sources, including patient registries and external clinical experts. The results of the targeted literature review showed that there is often a limited pool of clinical experts in a limited number of specialist centers [16,24]. It therefore is more challenging to identify external experts who can validate the health states, data inputs, and assumptions for models of rare diseases than for models developed for more prevalent conditions. Rodriguez-Monguio et al. [27] and Simoens [24] identified a number of potential challenges associated with patient registries, including restrictions due to data ownership, limited comparator data, and potential biases if disease severity changes over time.

A number of the identified studies underscored the challenges in achieving standard cost per QALY threshold in rare diseases, including Drummond et al. [5], Hughes-Wilson et al. [28], Schuller et al. [19], and Drummond et al. [29]. The targeted literature also showed that only limited information on the direct and indirect cost burden of an orphan disease may be available [28], making it difficult to estimate the potential economic benefit of treatment.

A number of studies discussed an issue with high drug acquisition costs because of sales to a limited number of patients [5,19,28]. In addition, many rare diseases are congenital or chronic; therefore, drug acquisition costs may accumulate with time [30]. Gutierrez et al. [26] also reported limited information on the additional health care costs associated with poorly controlled rare diseases.

Drummond et al. [29] and Gutierrez et al. [26] suggested that traditional outputs for economic models, including QALYs and disability-adjusted life-years, may not be sensitive to the severity of rare diseases. This may be explained by the smaller populations with severe disease and by the proportionally smaller improvements in health outcomes that in turn generate smaller QALY gains than would be the case in larger, healthier populations. In addition, the assumption that a QALY is of equal value, irrespective of indication, may not adequately reflect societal preferences for the treatment of life-limiting rare diseases. Finally, the benefits of patients or caregivers returning to work or school may not be captured by traditional model outputs [31].

Although some HTA bodies may not consider traditional threshold values, such as cost per QALY gained, when evaluating a drug for a rare disease, HTA bodies often do consider the effect of the treatment on the quality of life of patients and patient caregivers. Many rare diseases have an onset in childhood, resulting in a high burden to family caregivers [22]. Utility-weight data required to calculate incremental cost per QALY gained may be missing or limited [32], often owing to difficulties in patient recruitment [33] or from misplaced concern for increasing patient burden on answering questionnaires.

Targeted Review of NICE HST and SMC Ultra-orphan Submissions

We identified 3 NICE HSTs and 11 SMC ultra-orphan appraisals (Table 4) that were consistent with our criterion for publication dates. Detailed information on each of the models' methods, results, strengths, and limitations can be found in the Supplementary Appendix (Supplemental Tables 1–3), respectively. Many of the limitations identified by the HTA bodies were consistent with those identified in the targeted review, for example, limited available cost and utility-weight data [34], clinical evidence being restricted to nonrandomized studies with very small sample sizes [35], trials with no comparator arm [36], or short trial durations [36].

The targeted literature review highlighted a number of strategies that manufacturers employed to demonstrate product value for drugs that have limited clinical and economic evidence. The model developed for the elosulfase alfa in mucopolysaccharidosis type IVa (MPS-IVa) NICE HST submission [36] used the Delphi technique to assess the applicability of the model's utility values and to validate some of its assumptions. This widely used technique aims to achieve group consensus on a number of

Table 3 – Challenges identified in the targeted literature review that impact modeling in rare diseases.

Challenge	Source
Clinical evidence	
▪ Challenges in developing randomized clinical trials, a gold-standard clinical evidence source [14], in rare diseases because of limited patient numbers across global locations	Drummond et al. [5]; Morel et al. [15]; Korn et al. [20]; Schlander et al. [21]; Hughes-Wilson et al. [28]; Drummond and Evans [29]; McCabe et al. [49]
▪ Limited understanding of natural history and epidemiology of rare diseases and how this can affect trial design	Morel et al. [15]; Schlander et al. [16]; Wagner et al. [22]; Schlander et al. [21]; Simoens [24]; Hughes-Wilson et al. [28]; Gutierrez et al. [26]; Silva and Sousa [32]
▪ Limited number of physicians with specialized expertise in a limited number of centers	Schlander et al. [16]; Schlander et al. [21]; Simoens [24]
▪ Inadequately powered trials because of limited patient numbers, leading to higher levels of uncertainty with effect size	Morel et al. [15]; Schlander et al. [16]; Nicod [17]; Schuller et al. [19]; Schlander et al. [21]; Janoudi et al. [50]
▪ Total trial population and/or subgroup population heterogeneity	Morel et al. [15]; Nicod [17]
▪ Trial population inconsistent with required model population	Nicod [17]
▪ Imbalances in patient characteristics between trial arms	Nicod [17]
▪ Key clinical trial may not include a control arm because of ethical concerns.	Morel et al. [15]; Korn et al. [20]; Simoens [24]
▪ Limited effective comparators and comparator data	Nicod [17]; Wagner and Khoury [22]; Simoens [24]; Gutierrez et al. [26]
▪ Use of surrogate endpoints or biomarkers rather than "hard" clinical outcomes	Morel et al. [15]; Schlander and Garattini [16]; Nicod [17]; Schuller et al. [19]; Korn et al. [20]; Schlander et al. [21]; Silva and Sousa [32]; Paulden et al. [31]; Janoudi et al. [50]
▪ Limited availability and number of validated instruments to assess disease severity and progression	Schlander et al. [16]; Schlander et al. [21]
▪ Trials may be stopped early on ethical grounds based on interim data.	Simoens [24]
▪ Limited trial durations with slowly progressive or chronic rare diseases	Nicod [17]; Schuller et al. [19]
▪ Incomplete efficacy and safety profiles of treatments at product launch	Drummond et al. [5]; Schlander et al. [16]; Silva and Sousa [32]
Patient registries	
▪ Potential challenges with data ownership	Rodriguez-Monguio et al. [27]
▪ Patient registries may be biased if disease severity changes over time.	Simoens [24]
▪ Patient registries may not collect data on alternative orphan drug treatments.	Simoens [24]
Economic evidence	
▪ Limited information on the direct and indirect cost burdens of an orphan disease	Hughes-Wilson et al. [28]
▪ Challenges in achieving standard cost per QALY thresholds	Drummond et al. [5]; Schlander et al. [16]; Schlander et al. [21]; Simoens [24]; Hughes-Wilson and Palma [28]; Abrahamyan et al. [51]
▪ High drug costs from sales to a limited number of patients	Drummond et al. [5]; Schuller et al. [19]; Simoens [24]; Hughes-Wilson et al. [28]
▪ Congenital or chronic rare diseases will have drug-acquisition costs that accumulate with time.	Luzzatto et al. [30]
▪ QALYs and DALYs may not be sensitive to the disease severity of the patient population.	Gutierrez et al. [26]; Drummond et al. [29]
▪ Limited information available on the additional health care costs associated with poorly controlled disease.	Gutierrez et al. [26]

DALY, disability-adjusted life-year; QALY, quality-adjusted life-year.

stated questions about a particular topic via a group communication process [37]. This technique has been used previously in rare disease HTA submissions to ascertain transition probabilities for health-state models and to validate health-related quality-of-life values leveraged from other diseases. The model structure, clinical parameters, and assumptions also were validated by UK clinical specialists in the management of MPS-IVa and health economics experts.

The NICE Evidence Review Group (ERG) that reviewed the elosulfase alfa MPS-IVa HST submission was not aware of any other existing economic model for this indication; they noted that this was consistent with the manufacturer's statement that the model structure was informed by expert clinical opinion due to limited existing economic evidence [36]. Elosulfase alfa was recommended by NICE according to the conditions described in the published managed-access agreement [36].

The NICE HST submission for eculizumab in atypical uraemic syndrome (aHUS) included a recent UK survey that provided information on the burden of the disease for patients as well as their families [35]. Patients completed the surveys themselves; if the patient was a child, responses were completed on their behalf by a parent or caregiver. A total of 37 patients with aHUS

completed the survey. In addition, a physician survey was used to confirm UK standard of care and standard-of-care outcomes for aHUS. The ERG stated that the patient survey was one of the strengths of the submission [35]. The ERG also highlighted some of the findings of the patient survey, including the impact of aHUS on patient productivity, education, and day-to-day activities, as well as the potential for psychological distress of individuals who provided care for aHUS patients. However, the ERG also noted that nonscientific information from the patient survey was included in the submission dossier. NICE recommended that eculizumab's use should be coordinated with an expert center and that monitoring should be conducted to record the number of patients with aHUS, the number of patients receiving eculizumab, and the dose and duration of the treatment. NICE also recommended that a national protocol be developed for starting and stopping eculizumab for clinical reasons, as well as a research program to evaluate when to stop treatment or adjust dosage [35].

The SMC submission for lenvatinib, used to treat adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine, contained a match-adjusted indirect comparison (MAIC) of lenvatinib versus sorafenib for progression-free and overall survival outcomes [38]. This type of comparison can be used to account for differences in patient characteristics, provided at least one patient-level data set is available [39–42]. The SMC noted in its advice that the validity of the MAIC may be limited by a number of factors, including heterogeneity in inclusion criteria, assessment of disease progression, and analysis of progression-free survival across the studies [38]. The SMC also noted that there was insufficient detail to compare all possible confounding patient baseline characteristics. Furthermore, the MAIC failed to adjust for unobserved confounding factors or factors not observed in both studies. The MAIC results were not incorporated in the base-case economic analysis. The SMC's recommendation for lenvatinib was contingent on the availability of a Patient Access Scheme [38].

Conclusions

In a number of European markets, orphan drug products must undergo formal HTA economic evaluation following regulatory approval, to gain reimbursement status. The Good Practice Guidelines from the International Society for Pharmacoeconomics and Outcomes Research [43] and NICE's *Guide to the Methods of Technology Appraisal* [44] recommend the systematic pursuit of clinical and economic data and the application of robust methodologies in the development of economic models. Robust methodologies include reporting the rationale for any assumptions used in the model and performing extensive sensitivity and scenario analyses to explore the impact of structural and input parameter uncertainty. In rare diseases, however, a number of different factors may impact on the ability to comply with these good practice recommendations. These factors can vary by orphan indication: for instance, the long-term cost-effectiveness of an orphan product used to treat a congenital disorder in infants will be more challenging to estimate than the long-term cost-effectiveness of an orphan product used to treat an elderly population.

In this study, targeted reviews of PubMed, NICE HSTs, and SMC ultra-orphan submissions were used to identify the challenges that may affect models in rare diseases and the strategies manufacturers have used to demonstrate value of drugs that have limited study data.

Many treatments of rare diseases have a limited efficacy and safety profile at product launch [5], in part because of the smaller number of patients available for recruitment to trials in these diseases, and some HTAs require additional data collection post-launch to confirm the clinical benefit of treatment and to reduce uncertainty [45].

Our targeted literature review revealed that there is often limited available natural history and epidemiology data for rare diseases [26,28]. This affects the selection of the potential health states and input data for a cost-effectiveness model and can lead to uncertainty in the potential budget impact of a new drug for a rare disease [45].

The targeted literature review showed that clinical trials in rare diseases often are of a short duration [17], and controlled or direct head-to-head trials may not exist [20,29]. Furthermore, trials often consist of a single arm; if a placebo or standard-of-care arm is present, patients may be switched to the active treatment arm. If clinical data are limited, patient registry data may be required to provide clinical data for the comparator (i.e., standard-of-care) arm. Access to long-term registry data can provide modelers with an understanding of the natural history data of a rare disease; such data can be used as a surrogate for standard of care in the absence of placebo data. Even summary patient data from a patient registry will be advantageous: these data can be analyzed, alongside the patient-level data from the clinical trial, using a MAIC approach [39–42]. Such a comparison can be used to account for the different patient characteristics between a real-world registry data and a clinical trial's patient data. Although there are limitations to using registry data, such as the subjective matching of variables, these limitations should not be cited as a reason why patient registry data was not considered and their data analysis not undertaken.

Many rare diseases have an onset of illness in childhood, resulting in a high burden on family caregivers [22]. It is important to consult patients, their caregivers, any patient advocacy groups, and clinical experts early in the model development to ensure that the model structure adequately reflects the rare disease and captures the costs and clinical consequences. This consultation process can be used to confirm both the outcome measures that are relevant and the level of improvement that is clinically meaningful [45]. Clinical validation of an economic model structure is always recommended [46], and this is even more essential in a rare disease area where there is a lack of published information. Clinical experts also may know of potential data sources that may be made available, such as hospital-based activities that could provide accurate patient-level health care resource-use data for the model. In addition, both clinical experts and patient groups can help provide prevalence and potential uptake of treatment estimates [45].

The value of patient advocacy groups should not be underestimated. Patient advocacy groups are eager to understand new treatments and can provide valuable insight into what patients deem to be important—which may differ from clinical opinion. Patient advocate groups also can provide access to patients and their caregivers, which is crucial for quality-of-life and resource-use data-collection studies.

In addition to advising on potential data sources, clinical opinion can be sought, via means of a Delphi process, on parameter values within the economic model. This widely used technique aims to achieve group consensus on a number of stated questions about a particular topic via a group communication process [37]. This technique has been used previously in rare disease HTA submissions to ascertain transition probabilities for health-state models and to validate health-related quality-of-life values leveraged from other diseases [36]. Where a paucity of data exist, clinical opinion also should be sought on the use of published data, for example, on health care resource-use and quality-of-life data, from a more prevalent but similar disease. Take, for example, multiple sclerosis compared to Duchenne's disease or MPS-IVa. These are muscular wasting diseases in

Table 4 – Identified NICE HST and SMC PACE ultra-orphan appraisals.

Author, year	Product	Indication	HTA appraisal	Recommendation
National Institute for Health and Care Excellence [34], 2016	Ataluren	For treating DMD with a nonsense mutation in the dystrophin gene in people aged 5 years and older who can walk	NICE HST 3	Ataluren, within its marketing authorization, is recommended for treating DMD resulting from a nonsense mutation in the dystrophin gene in people aged 5 years and older who can walk, only when: • The company provides ataluren with the discount agreed upon in the PAS. • The conditions under which ataluren is made available are set out in the managed-access agreement between the company and NHS England, which should include the conditions set out in Sections 5.12–5.15 and 5.23 of this guidance. This guidance is not intended to affect the position of patients whose treatment with ataluren was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.
National Institute for Health and Care Excellence [35], 2015	Eculizumab	For treating aHUS in adults and children	NICE HST 1	Eculizumab, within its marketing authorization, is recommended for funding for treating aHUS, only if all the following arrangements are in place: • Coordination of eculizumab use through an expert center • Monitoring systems to record the number of people with a diagnosis of aHUS and the number who are prescribed eculizumab, and the dose and duration of treatment • A national protocol for starting and stopping eculizumab for clinical reasons • A research program with robust methods to evaluate when stopping treatment or dose adjustment might occur The long-term budget impact of eculizumab for treating aHUS is uncertain but will be considerable. NHS England and the company (Alexion Pharma UK) should consider what opportunities might exist to reduce the cost of eculizumab to the NHS.
National Institute for Health and Care Excellence [36], 2015	Elosulfase alfa	For treating MPS-IVa in adults and children	NICE HST 2	Elosulfase alfa, within its marketing authorization, is recommended for funding for treating MPS-IVa according to the conditions in the managed-access agreement for elosulfase alfa.
Scottish Medicines Consortium [11], 2016	Ataluren	Treatment of DMD resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older	SMC PACE	Ataluren is not recommended for use within NHS Scotland. This advice takes into account the views expressed during a PACE meeting.

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Scottish Medicines Consortium [52], 2016	Bevacizumab	In combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan in patients, for the treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix	SMC PACE	Accepted for restricted use within NHS Scotland. Restriction: for use in combination with cisplatin and paclitaxel This advice takes account of the benefits of a PAS that improves the cost-effectiveness of bevacizumab. This advice is contingent on the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower. This advice takes account of the views expressed during a PACE meeting.
Scottish Medicines Consortium [53], 2016	Blinatumomab	The treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor ALL	SMC PACE	Accepted for use within NHS Scotland. This advice takes account of the views expressed during a PACE meeting. This SMC advice takes account of the benefits of a PAS that improves the cost-effectiveness of blinatumomab. This advice is contingent on the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.
Scottish Medicines Consortium [54], 2016	Ceritinib	Treatment of adult patients with ALK-positive advanced NSCLC previously treated with crizotinib	SMC PACE	Accepted for use within NHS Scotland. This advice takes account of the benefits of a PAS that improves the cost-effectiveness of ceritinib. This advice is contingent on the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower. This advice takes account of the views expressed during a PACE meeting.
Scottish Medicines Consortium [55], 2016	Crizotinib	First-line treatment of adults with ALK-positive advanced NSCLC	SMC PACE	Accepted for use within NHS Scotland. This advice takes account of the views expressed during a PACE meeting. This SMC advice takes account of the benefits of a PAS that improves the cost-effectiveness of crizotinib. This advice is contingent on the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.
Scottish Medicines Consortium [56], 2016	Eculizumab	Treatment of children and adults with PNH	SMC PACE	Not recommended for use within NHS Scotland. This advice takes account of the views expressed during a PACE meeting.
Scottish Medicines Consortium [57], 2016	Eculizumab	In adults and children for the treatment of patients with aHUS	SMC PACE	Not recommended for use within NHS Scotland. This advice takes account of the views expressed during a PACE meeting.
Scottish Medicines Consortium [58], 2016	Ibrutinib	Treatment of adult patients with relapsed or refractory mantle cell lymphoma	SMC PACE	Accepted for use within NHS Scotland. This SMC advice takes account of the benefits of a PAS that improves the cost-effectiveness of ibrutinib. This advice is contingent on the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower. This advice takes account of the views expressed during a PACE meeting.

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Table 4 – *continued*

Author, year	Product	Indication	HTA appraisal	Recommendation
Scottish Medicines Consortium [59], 2016	Ivacaftor	Treatment of children with cystic fibrosis aged 2 years and older and weighing less than 25 kg who have one of the following gating (class III) mutations in the cystic fibrosis transmembrane conductance regulator gene: *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N*, or *S549R*	SMC PACE	Not recommended for use within NHS Scotland. This advice takes account of the views expressed during a PACE meeting.
Scottish Medicines Consortium [38], 2016	Lenvatinib	Treatment of adult patients with progressive, locally advanced or metastatic differentiated (papillary/follicular/ Hürthle cell) thyroid carcinoma refractory to radioactive iodine	SMC PACE	Accepted for use within NHS Scotland. This SMC advice takes account of the benefits of a PAS that improves the cost-effectiveness of lenvatinib. This advice is contingent on the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower. This advice takes account of views expressed during a PACE meeting.
Scottish Medicines Consortium [60], 2016	Trametinib	In combination with dabrafenib for the treatment of adult patients with unresectable or metastatic melanoma with a *BRAF* V600 mutation	SMC PACE	Accepted for restricted use within NHS Scotland. SMC restriction: to first-line treatment This advice takes account of the benefits of PAS that improve the cost-effectiveness of trametinib and dabrafenib. This advice is contingent on the continuing availability of these patient access schemes in NHS Scotland or list prices that are equivalent or lower. This advice takes account of views expressed during a PACE meeting. Trametinib is also licensed as monotherapy. As the company submission related only to combination therapy, SMC cannot recommend use as monotherapy.

aHUS, atypical hemolytic-uremic syndrome; ALK, anaplastic lymphoma kinase; ALL, acute lymphoblastic leukemia; DMD, Duchenne muscular dystrophy; HST, highly specialized technology; HTA, health technology assessment; MPS-Iva, mucopolysaccharidosis type IVa; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NSCLC, non–small-cell lung cancer; PACE, Patient and Clinician Engagement; PAS, Patient Access Scheme; PNH, paroxysmal nocturnal hemoglobinuria; SMC, Scottish Medicines Consortium.
Note: All information presented in this table is as reported in the HTA sources.

which ambulatory movement decreases and the need for wheelchair increases as the disease progresses. The need for wheelchairs for patient movement and the impact on the patients' quality of life could be considered similar across these diseases, and values for the more prevalent disease (multiple sclerosis) could be leveraged for the rare diseases (Duchenne's disease and MPS-IVa) [36].

Further, given the high acquisition costs of drugs to treat rare diseases, clinical expert opinion can be used to inform potential stopping rules in instances when treatment is no longer effective, and to determine how these rules will be implemented in clinical practice.

To support the development of models for markets that require an estimate of the incremental cost per QALY gained, utility data will be required. If utility data have not been collated directly in the clinical trial, mapping from quality-of-life questionnaires that were part of the clinical trial may be required. If suitable utility weights are not available from the literature, the manufacturer may need to commission a utility-weight study for the indication of interest or for an analogue condition. If patients cannot complete a utility-weight questionnaire themselves, the use of proxies, that is, family caregivers or even clinicians, may be required, just as proxies are often necessary in studies of non-orphan conditions such as Alzheimer's disease [47]. Family member and/or caregiver disutility also can be considered in a commissioned utility-weight study.

In addition to these data considerations, it is important to note other factors that are important to patients with rare diseases, to their caregivers, and to their clinicians, such as the potential for a new intervention to improve patient independence and/or increase his or her ability to work.

While these approaches can bridge the gaps in the evidence base, it also is important to follow best practice and perform extensive sensitivity and scenario analyses to explore the impact of structural and data input uncertainties. Where data uncertainties exist, managed-access agreements between payers and pharmaceutical companies, such as the UK Cancer Drugs Fund [48], may be used as a data collection mechanism to resolve uncertainty relating to clinical and cost-effectiveness.

Recommendations

A number of recommendations can be made to help demonstrate the value of orphan products with limited study data. Where relevant, the rationale should be clearly presented as to why best practices in economic modeling cannot be followed. Patient experience information and clinical opinion should be collated in a systematic manner. The value of information should be estimated to inform data-collection priorities. Updates to the economic model should be planned to validate model assumptions using collated, real-world data. These approaches will help manage uncertainty and optimize the rigor of an economic evaluation in rare diseases.

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Supplemental Materials

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