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Economic Modeling Considerations for Rare Diseases

Isobel Pearson, DPhil[1], *Ben Rothwell, MSc*[1], *Andrew Olaye, PhD*[2], *Christopher Knight, MSc*[1,*]

[1]*RTI Health Solutions, Manchester, UK;* [2]*Pharma Consultant, London, UK*

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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*Address correspondence to: Christopher Knight, RTI Health Solutions, The Pavilion, Towers Business Park, Wilmslow Road, Didsbury, Manchester, M20 2LS, UK.

E-mail: cknight@rti.org.

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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