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Dealing with Uncertainty and Accounting for Social Value Judgments in Assessments of Orphan Drugs: Evidence from Four European Countries

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ABSTRACT

Objectives: To better understand the reasons for differences in reimbursement decisions for orphan drugs in four European countries that were not readily apparent from health technology assessment (HTA) reports and operating procedures. **Methods:** Semistructured interviews with representatives of HTA bodies in England, Scotland, Sweden, and France were conducted. An interview topic guide was developed on the basis of findings from a systematic comparison of HTA decisions for 10 orphan drugs. Qualitative thematic data analysis was applied to the interview transcripts using the framework approach. **Results:** Eight representatives from the four HTA bodies were interviewed between March and June 2015. Evidentiary requirements and approaches to dealing with imperfect or incomplete evidence were explored, including trial design and duration, study population and subgroups, comparators, and end points. Interviewees agreed that decisions regarding orphan drugs are made in a context of lower quality evidence, and the threshold of acceptable uncertainty varied by country. Some countries imposed higher evidentiary standards for greater clinical claims, which may be more challenging for orphan diseases. The acceptability of surrogate end points was not consistent across countries nor were the validation requirements. The most common social value judgments identified related to innovation, disease severity, and unmet need. Differences were seen in the way these concepts were defined and accounted for across countries. **Conclusions:** Although agreement was seen in evidentiary requirements or preferences, there were subtle differences in the circumstances in which uncertain evidence may be considered acceptable, possibly explaining differences in HTA recommendations across countries.

Keywords: health technology assessment, orphan drugs, rare diseases, value assessments.

Introduction

Health technology assessment (HTA) aims to ensure that technologies offered are safe and efficacious and provide value for money [1]. Although value is often considered within the context of efficiency—reimbursing only the most efficient technologies within an allowable budget—this does not necessarily account for what matters most to patients or to society in general [2]. Indeed, certain aspects of value are difficult to capture and yet may provide benefits to both, such as innovation that results in a direct benefit to patients through improved prognosis or quality of life and also indirect societal benefits in terms of increased productivity and knowledge spillovers.

Despite using the same evidence and similar outcome measures and criteria, HTA assessments of a given drug may lead to contrary results in different countries [3]. This is particularly true with respect to orphan drugs, for which the general rules regarding appropriate evidence may be difficult to apply to small populations facing very serious chronic or life-limiting diseases [4]. Orphan drug trials are often characterized by lower quality evidence compared with nonorphan drugs [5,6]. Moreover, high acquisition costs often result in orphan drugs not being found to be cost-effective [7]. Nonetheless, orphan drugs often undergo the same HTA processes as drugs for more prevalent conditions.

In the face of imperfect evidence and high uncertainty in assessing orphan drugs, HTA bodies may rely on different attributes of value or approaches to dealing with imperfect evidence. Acceptability of uncertainty depends on the tools used to address uncertainty and on the judgment of the decision makers, who may consider additional qualitative criteria, such as disease or treatment characteristics [8].

Understanding the rationales underlying conflicting decisions is challenging. Although the internal regulations of HTA bodies explain the operating framework and the opinions or recommendations document the evidence considered and the basis for the decision, certain subtleties may not be captured even in the most complete documentation. A better understanding is therefore needed about how HTA bodies value orphan drugs and deal with issues of rarity.

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We previously analyzed the decisions of 4 HTA bodies for 10 orphan drug-indication pairs on the basis of the opinions and in light of each entity's internal regulations [9], and we explored scientific and social value judgments used in the assessment of orphan drugs [10]. A number of reasons for differences in HTA recommendations were identified throughout the decision process and across countries. Building on these findings, this study aimed to develop a broader perspective about how value is assessed for orphan drugs and how differences affect reimbursement decisions on the basis of interviews of representatives of four European HTA bodies.

Methods

Purposeful sampling was used to select the study countries, each of which undertakes assessments using well-established processes and criteria, has publicly available reports, and represents a cross selection in terms of HTA approach and perspective (Table 1). These included the National Institute for Health and Care Excellence (NICE, England), the Scottish Medicines Consortium (SMC, Scotland), the Dental and Pharmaceutical Benefits Board (Tandvårds- och läkemedelsförmånsverket, Sweden), and the French National Authority for Health (*Haute Autorité de Santé* [HAS], France). HTA body representatives from each study country were identified by partners of a European research consortium, Advance-HTA [11]. These HTA bodies have either regulatory or advisory roles, in which their decisions will be automatically implemented in the former and accounted for by the final decision maker in the latter (Table 1). Furthermore, orphan drugs do not have a special status in the study countries, with the exception of SMC, in which greater uncertainty or higher incremental cost-effectiveness ratios (ICERs) may be accepted if the requirements for their modifiers are fulfilled [12].

We conducted semistructured interviews using an interview topic guide developed by the lead author and reviewed by all co-authors (see eAppendix A in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.03.005). It included open-ended questions derived from actual scenarios that arose in the context of our cross-national comparison of 10 orphan drugs. Interview questions were divided into themes, including 1) the general evidentiary requirements for orphan drugs regarding primary and nonprimary evidence, trial duration, and clinical and surrogate end points; 2) other evidence and considerations around quality-of-life data and qualitative critera (innovation, unmet need, and disease severity) and the consistency in the considerations across decisions; 3) dealing with uncertainty relating to orphan drug characteristics; and 4) stakeholder involvement. An email invitation to participate in a face-to-face or telephonic interview along with the topic guide was sent to each interviewee. Anonymity was assured, and interviews were recorded and transcribed and sent to the interviewees for comment and validation. The study protocol was reviewed pursuant to the London School of Economics Research Ethics procedure and was found to be exempt (see eAppendix B in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.03.005).

Qualitative thematic data analysis was undertaken using the framework approach [13]. Subthemes within each general theme were identified and inductively coded, and a matrix was created to facilitate comparison of each subtheme across the four HTA bodies. The key findings from each of these subthemes were summarized in tables that incorporated illustrative quotes. The initial findings were discussed among the co-authors, and a list of follow-up questions was developed to complement the interviews in which information was unclear or incomplete. These additional questions were sent to each interviewee along with the summary findings for their particular HTA body for confirmation. Results focused on the contrasts across countries identified within each theme. Themes were reorganized as follows: 1) clinical evidence and uncertainty, 2) comparators, 3) treatment outcomes and safety, and 4) additional qualitative criteria.

Each theme portrays the agencies' perspectives about the clinical evidence appraised and whether evidence for orphan drugs is characterized by greater uncertainty compared with drugs for more prevalent conditions. The evidence base used for HTA is imperfect or incomplete, and therefore uncertain, because it relies on estimated values from experimental or observational studies [14–16]. Decision makers make scientific value judgments about the extent to which uncertain evidence is acceptable. These judgments include whether the evidence presented fully and accurately captures the effect of the intervention, whether it is generalizable to the local context of the decision, whether quality-of-life changes are accurately captured, or whether it is appropriate to impose restrictions to population subgroups [14]. We aimed to obtain additional insights on the appraisal processes in terms of the HTA bodies' approaches to dealing with uncertain evidence, including the circumstances under which imperfect or incomplete evidence that does not accurately capture the effect of the intervention may be deemed acceptable.

Results

Eight representatives from the four HTA bodies were interviewed between March and June 2015. Interviewees occupied senior positions in their agencies (e.g., Head of the Technology Appraisal Programme, Head Economist or Pharmacist, and Chair of the Appraisal Committee). Interviews were conducted face-to-face and, in one case, by telephone, lasting 1 to 3.5 hours. Responses are summarized in Figures 1 and 2 and presented in Table 2,

Table 1 – Study countries, HTA bodies, and types of HTA.

Study country	HTA body	Type of HTA
England	NICE: National Institute for Health and Care Excellence (regulatory body)	Clinical and cost-effectiveness, national health and personal social services perspective
Scotland	SMC: Scottish Medicines Consortium (advisory body to the NHS boards)	Clinical and cost-effectiveness, national health and personal social services perspective
Sweden	TLV: Dental and Pharmaceutical Benefits Board (regulatory body)	Clinical and cost-effectiveness, societal perspective
France	HAS: Haute Autorité de Santé (Comité de la Transparence) (advisory body to the Ministry of Health)	Benefit-risk ratio, clinical benefit driving the coverage rate (SMR), and relative improvement in clinical benefit driving the pricing scheme (ASMR)

ASMR, relative improvement in clinical benefit ("Amélioration du Service Médical Rendu"); HTA, health technology assessment; NHS, National Health Service; SMR, clinical benefit ("Service Médical Rendu").