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Scientific and social value judgments for orphan drugs in HTA

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Short title: Scientific and social value judgments in HTA

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Abstract

Objectives.

We explore how broader aspects of a treatment's value and the impact of the condition on patients not captured by routine Health Technology Assessment (HTA) methods using clinical and economic evidence, defined as "other considerations", may influence HTA processes in different settings.

Methods.

Countries included were England, Scotland, Sweden, and France. Data sources were the publicly available reports on HTA recommendations. Ten drugs with EMA orphan designation and appraised in England were selected. Qualitative thematic analysis was used to systematically identify and code all "other considerations" based on a previously validated methodological framework, which also coded whether it was provided by stakeholders, and how it influenced the decision.

Results.

A classification framework of scientific and social value judgments was developed and used throughout the study. 125 "other considerations" were identified and grouped into ten subcategories based on the information provided. 18% to 100% of these, depending on the agency, were put forward as one of the main reasons for the final decision potentially contributing to accepting a higher ICER or uncertain evidence. Some of these were non-quantified or non-elicited and pertained to the assessor's judgment. A taxonomy of these value judgments was created to be used in future cases. Results also contributed to better defining the determinants of social value and improving accountability for reasonableness.

Conclusions.

The systematic identification of the scientific and social value judgments enables to better understanding the dimensions of value, which can be used to improve their transparency and consistent use across decisions and settings.

Introduction

Healthcare decision-makers are responsible for resource allocation decisions with the primary objective to maximise health and social welfare in the whole population.(1) Health technology assessment (HTA) helps make such decisions about whether to reimburse a new treatment by providing guidance on the efficient use of resources, ultimately, optimising patient access to these. It relies on systematic approaches to appraising evidence about the value of using this treatment in terms of benefits (and costs) in real world settings, while including considerations of social, ethical and legal aspects to inform coverage for this technology.(2)

Routine HTA methods that rely on clinical (and economic) evidence may not adequately capture all the important considerations of a treatment's value and the impact of the condition on patients in real world settings.(3) This is partly because HTA is undertaken at the time of the treatment's launch onto the market when evidence is often incomplete since real world evidence is generally not available. HTA bodies also tend to rely on experimental evidence collected within controlled environments (e.g. RCTs),(4) despite their limitations in capturing effectiveness.(5) In such cases, scientific judgments about the reliability, generalisability and meaningfulness of this evidence in the clinical context are made.(6, 7) Additionally, these processes also account for elicited societal preferences that refer to cases when society agrees to forego health in order to treat specific populations. Yet, decision-makers may grant preference for a treatment despite this preference not having been previously elicited by the general population; these would be considered as social value judgments.(6, 7) These judgments are usually made as part of the deliberative process of HTA, during which experts and key stakeholders are consulted and the evidence is discussed until a decision is taken.(8) The main criticisms of this process is the lack of "accountability for reasonableness" given

that there is not always a clear process to account for the inclusion of these forms of evidence in the assessment process, as well as the lack of consistency in accounting for these "other considerations".(8-10)

Drugs used to treat rare conditions with an orphan designation are often characterised by uncertainty and high incremental cost-effectiveness ratios (ICER), and are usually not cost-effective.(11) This is a consequence of the difficulties in producing robust evidence due to the small patient populations and the heterogeneity of these conditions, as well as their high prices. These reimbursement decisions therefore rely on whether society is willing to forego health to the whole population in order to treat fewer patients with a rare condition.(12) Little evidence in support of a societal preference for rare conditions exists, and the few studies that attempted to elucidate this suggested the contrary when patients with more common diseases were denied treatment in order to treat fewer patients with a rare condition.(12-15) In such cases, these decisions partly rely on the decision-makers' willingness to accept high ICERs based on additional factors that influence their judgment of (scientific and social) value, such as, for example, disease severity, the treatment's orphan status, or to what extent evidence characterised by uncertainty is acceptable.(16) They also rely on the flexibility of these processes in, for example, their ability to implement managed entry agreements or the availability of separate funding programs (e.g. Cancer Drug Fund in England). It is somewhat different in France, where a procedure has been set up to expedite access to drugs for rare diseases, as a means to support development and dissemination of treatment for populations suffering from rare conditions.

This study goes beyond the assessment of clinical and economic evidence into other areas that help explain value. Its purpose is to explore how broader aspects of a treatment's value

and the impact of the condition on patients, not captured by routine HTA methods, influence these HTA processes in different countries. This is all the more important given that expectations from HTA bodies in terms of relative effectiveness may differ depending on drug and disease characteristics.(17) The subject of analysis was a sample of orphan drugs in four countries (England, Scotland, Sweden, and France), because of the greater uncertainty characterising these. We then examined whether the social value judgments revealed pertain to orphan drugs and under what circumstances do they have a preferential status.

Methods

Study sample

Purposive sampling was used to select the study countries with the aim of having a good representation of different types of decision-making characteristics, in terms of: (a) the criteria used; (b) the perspective adopted; and (c) any existing elicited preferences (Table 1). The HTA agencies and their decision-making Committees included were: the Appraisal Committee of the National Institute for Health and Care Excellence (NICE) in England, the Scottish Medicines Consortium (SMC) in Scotland, the Dental and Pharmaceutical Benefits Board (TLV) in Sweden, and the Transparency Committee of the Haute Autorité de Santé (HAS) in France. HAS assesses the drug's medical benefit (Service Médical Rendu, SMR) to inform its coverage rate and the relative improvement in medical benefit (Amélioration du Service Médical Rendu, ASMR) to inform the pricing negotiation, ranking treatments in five levels. Both the drug's medical effectiveness (risk-benefit ratio) and its interest in terms of public health (ISP) are accounted for in the SMR assessment. No economic modelling was done by HAS at the time of the sampled drugs' appraisals. For cost considerations, NICE and SMC agencies adopt a health service perspective and TLV a societal perspective.

Ten drug and indication pairs were selected, with the following criteria: (a) with an orphan drug designation from the European Medicines Agency, (b) appraised by the NICE Single Technology Appraisal process until December 2012, and (c) by at least two other study countries.

Data collection and analysis

This empirical study applied a validated methodological framework enabling the systematic identification and comparison of the criteria driving HTA decisions for the same drugs in different countries through a mixed methods research design comprising three key stages: the evidence appraised, its interpretation and its influence on the final recommendation.(17) In this paper, we focus on the results from the interpretation of the evidence component. Specifically, we wanted to see what elements beyond cost-effectiveness, cost, effectiveness and safety were raised by the HTA agencies and whether these played a role on the decision-making.

Thematic analysis was conducted to identify and code all the "other considerations" accounted for during the appraisal process and recorded in the appraisal reports. Bottom-up coding was performed, where codes were inductively created while examining the data to summarise what was put forward and categorise this data depending on the type of information provided.(18) The section of text coded included all the text referring to the "other consideration". For example, the whole section of text referring to the scarcity in the treatments alternatives available would be coded as "few treatment alternatives". Codes were then categorised into subcategories depending on the type of information provided, and

recorded in a coding manual.(17) These were clustered into two groups: disease characteristics and treatment characteristics. Coding was iterative and flexible to ensure the transferability of codes to other drugs and countries, and additional codes were created with newly identified "other considerations". Coding was conducted by the lead author. Coding reliability was tested by a colleague expert in Health Policy, who re-categorised each individual code into one of these. Where differences were observed, adjustments were made and documented. The validity of the data collected was established through feedback from external experts, including from HTA bodies (who have been presented most of this work), HTA experts from the Advance-HTA Consortium, and fellow peers when presented at conferences.

Coding was performed vertically and horizontally. In the former, all "other considerations" were coded in a systematic manner as prescribed in the coding manual(17). In the latter, all "other considerations" were double coded with: (a) if it was put forward as one of the main reasons for the decision, (b) source of the information provided (e.g. experts), and (c) if it was accounted for in the other countries. The data collected qualitatively was then quantitatively analyzed to determine: (a) the type and frequency of "other considerations" accounted for; (b) cases when these were one of the main reasons for the decisions; (c) how they were provided; and (d) how they compared across agencies. The qualitative statistical software NVivo 10 was used for the data collection and analysis,(19) and Excel for further data analysis. Data sources consisted in the HTA reports publicly available from each HTA body, complemented with a selected review of the literature and input from key stakeholders (HTA bodies, Advance-HTA Consortium, other peers).

For each sub-category of "other considerations", we then explored whether they are more likely to pertain to orphan drug and rare disease characteristics, identified from key reports and official documents defining rare diseases and highlighting their common characteristics.(20, 21).

Results

Value judgment classification framework

When evidence is uncertain or incomplete, scientific value judgments are made about its acceptability. Societal preferences are also accounted for by HTA approaches. These pertain to giving preference to certain (non-quantifiable) aspects of living with a disease or taking a treatment, which are translated into prioritising certain groups of patients over others, which can be elicited or not.(6, 7) These preferences are typically elicited by a group of representative citizens (e.g. NICE's Citizens Council) or are enshrined within legislation. Examples of elicited preferences include the "SMC modifiers", or disease severity in Sweden defined "on the basis of the relevant, initial condition and risk of permanent injury, ultimately death without treatment. All the positive effects the medicine has on people's health and quality of life are accounted for".(22) Non-elicited preferences, referred to as social value judgments, originate from the individual appraisal committee member's value judgment based on their experience or on what they believe society would prefer, and are usually made as part of the deliberative processes of HTA. Both scientific and social value judgments are defined as "other considerations" within the scope of this study (Table 1).

Table 1. HTA bodies sampling and classification framework of scientific assessment and of social or societal preferences

HTA Body	**Scientific assessment**		**Social or societal preferences**			**ICER**
	HTA criteria & perspective *-quantified-*	**Scientific value judgments** *-non-quantified-*	**Preferential status** *-elicited-*	**Orphan drug preferential status** *-elicited-*	**Social value judgments** *-non-elicited-*	✔ Acceptable ★ Acceptable, accounting for other factors ✗ Not acceptable unless exceptional circumstances
England National Institute for Health and Care Excellence - NICE	Clinical cost-effectiveness (ICER) National Health Service (NHS) and Personal Social Services (PSS) perspective	As part of the deliberative process, judgment about the ***acceptability of uncertain or incomplete evidence***, including about the ***assumptions*** made (e.g. economic modelling), or about certain ***non-quantified*** considerations around treatment and disease characteristics. Examples: - health-related	End-of-life supplementary advice: - life-threatening - small patient numbers - life-extending		As part of the deliberative process, giving preference to certain ***non-quantifiable*** considerations around treatment and disease characteristics when these have not been elicited from a representative population of citizens. Preference originates from the individual judgments of the appraisal committee based on their ***experience*** or on ***what they believe society would prefer*** or on ***conclusions of***	✔ < 20,000/QALY ★ £20-£30,000/QALY ✗ > £30,000/QALY (e.g. end-of-life treatment)
Scotland Scottish Medicines Consortium - SMC	Clinical cost-effectiveness (ICER) National Health Service (NHS) and Personal Social Services (PSS) perspective			SMC modifiers: - life-threatening - life-extending - quality of life improvement - curative intent		✔ no threshold, but accounts for NICE threshold ★ no threshold, but accounts for NICE threshold ✗ no maximum threshold, but accounts for NICE threshold

		quality of life - administration benefits - uncertain resource use - clinical pathways - discount rate - disease severity		- unmet need	***citizen's councils / juries.*** Examples: - orphan status - unmet need - treatment innovativeness - disease severity	
Sweden Dental and Pharmaceutical Benefits Board - TLV	Human value, need and solidarity principle, and cost-effectiveness (ICER) Societal perspective		Disease severity & unmet need			✔ no threshold, but based on previous decisions average of drugs approved is Eur 36,000/QALY ★ no threshold, but based on previous decisions average of drugs approved is Eur 36,000/QALY, up to Eur 90,000/QALY ✗ no maximum threshold, but based on previous decisions ICER greater than EUR 90,000/QALY
France Haute Autorité de Santé - HAS	Clinical benefit (SMR) and relative improvement in clinical benefit (ASMR)			Public Health Act 2004, recognising rare diseases as a national priority		No threshold exists though a two-stage process is used where coverage relies on the clinical benefit (SMR) and the price negotiation uses the (relative) improvement in clinical benefit (ASMR).

Study drugs and HTA recommendation

The study included ten drugs for specific indications. The five inpatient drugs were not appraised by TLV, whom only appraised outpatient drugs at the time of the study. Based on the indicative cost-effectiveness thresholds (Table 1), some treatments with an ICER greater than the respective threshold received a positive recommendation: mannitol dry, azacitidine, lenalidomide, mifamurtide, and trabectedin for NICE; azacitidine, lenalidomide, mifamurtide, and imatinib for SMC; everolimus, mifamurtide and romiplostim for TLV. In some instances, the ICERs were improved with a Patient Access Scheme that provided a confidential discounted drug price. In France, where coverage is disconnected from the ICER and no threshold exists, only one case was rejected for reimbursement (mifamurtide), three drugs received an ASMR V where no additional benefit was recognised (ofatumumab, mannitol dry, trabectedin), and the remainder were considered to provide additional benefits (Table 2).

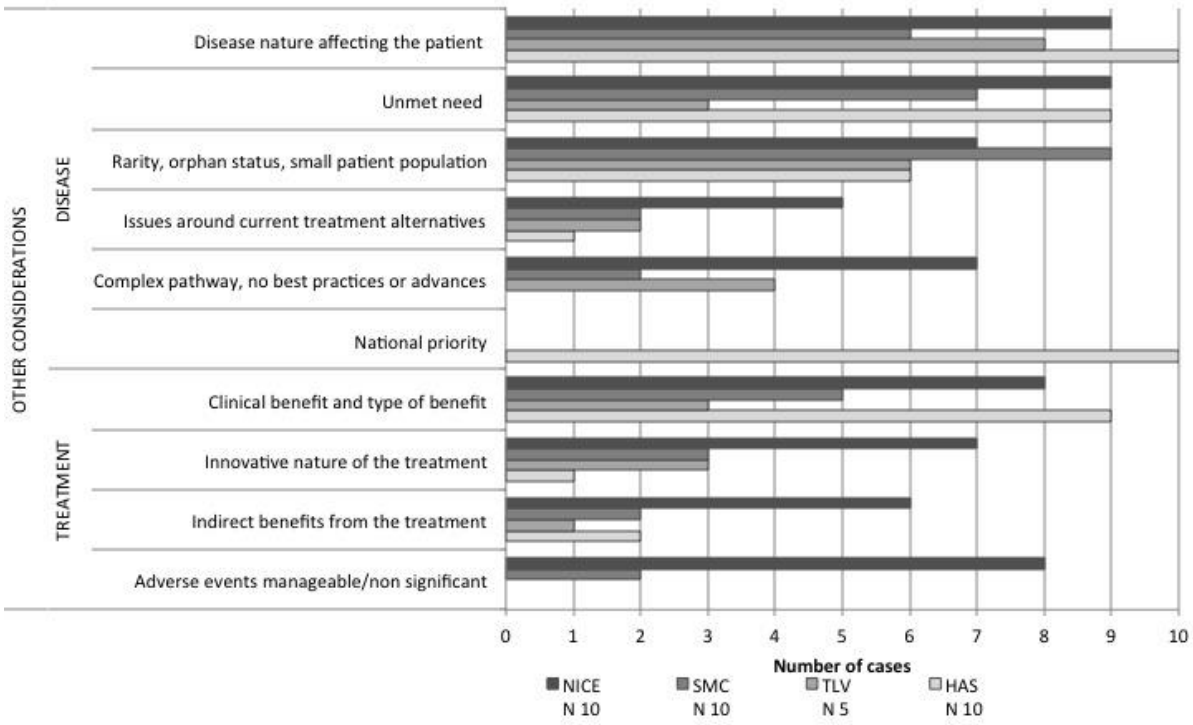
Table 2. ICER and coverage decisions (SMR and ASMR in France)

	NICE England		SMC Scotland		TLV Sweden		HAS France	
Drug Indication	**ICER**	**Decision**	**ICER**	**Decision**	**ICER***	**Decision**	**SMR**	**ASMR**
Eltrombopag Chronic thrombocytopenic purpura	✗ £104,000-£116,000/QALY (standard care)	**Reject**	✔CUA dominant compared to romiplostim (SMC modifiers)	**Restrict** (Subgroup severe ITP and high risk of bleeding)	✔CMA dominant compared to romiplostim (severity)	**Restrict** (Re-assessment, and for hospital	Important	**II**
Ofatumumab Chronic lymphocytic leukemia	✗ £50,300 - £81,500/QALY, depending on subgroup (PAS)	**Reject**	✗ £108,815/QALY	**Reject**			Moderate	**V**
Mannitol dry Cystic fibrosis	✗ £50-£80,000/QALY rhDNase ★< £30,000/QALY no rhDNase	**Restrict** (Subgroup with no rhDNase, rapid decline of lung function, intolerant to osmotic agents)	★£20,736/QALY no rhDNase	**Reject**			Weak	**V**
Everolimus Renal cell carcinoma (2nd line, advanced)	✗ £51,700/QALY (EoL, PAS)	**Reject**	✗ £61,330/QALY	**Reject**	★Cost/QALY high but justified given the severity of the disease (severity)	**List**	Important	**IV**
Azacitidine Myelodysplastic syndrome	✗ £47,200/QALY (best case scenario) (EoL, PAS)	**List**	✗ £51,275/QALY (SMC modifiers, PAS)	**List**			Important	**II**
Lenalidomide Multiple myeloma (2nd, 3rd line)	✗ two or more prior therapies: £41,300-43,800/QALY (chemo alone) (EoL, PAS)	**Restrict** (Subgroup 3rd line)	✗ £34,286-£41,381/QALY (chemo alone) (SMC modifiers)	**Restrict** (Subgroup 3rd line)	✔SEK290,000/QALY (bortezomib) = EUR 32,000/QALY (severity)	**List**	Important	**III**
Mifamurtide Osteosarcoma	✗ £36,000/QALY (1.5% discount, PAS)	**List**	✗ £48,579/QALY (1.5% discount, PAS)	**List**	★- ✗ SEK 700,000-900,000/QALY = EUR 77-99,000/QALY (severity, 3% discount)	**List**	Insufficient	**DNL**
Trabectedin Soft tissue sarcoma	✗ £34,500/QALY (EoL, PAS)	**List**	★£36,841/QALY (PAS)	**Reject**			Important	**V**
Imatinib Gastro-intestinal stromal tumours (GIST) (adj. unresectable and/or metastatic)	★£21-£23,000/QALY (significant and moderate risk of recurrence)	**Reject**	★£20,655/QALY (SMC modifiers)	**Restrict** (Subgroup of patients with high risk of recurrence following complete resection)			Important	**III**
Romiplostim Chronic thrombocytopenic purpura	✔High risk of bleeding < £20,000/QALY slenectomised = £30,000/QALY non-splenectomised (PAS)	**Restrict** (Subgroup with high risk of bleeding, risk management plan)	✔High risk of bleeding: £15,220/QALY splenectomised £16,673/QALY non-splenectomised (standard care) (SMC modifiers)	**Restrict** (Subgroup with high risk of bleeding, 2nd line or when surgery is contraindicated)	★SEK 400-600,000/QALY = EUR 44-66,000/QALY	**Restrict** (Re-assessment & risk management plan)	Important	**II**
✔	Acceptable ICER: - within 20,000/QALY for NICE. - SMC: no threshold, but accounts for NICE threshold - TLV: no threshold, but based on previous decisions average of drugs approved is Eur 36,000/QALY							
★	Acceptable ICER accounting for other factors: - NICE: £20-£30,000/QALY - SMC: no threshold, but accounts for NICE threshold - TLV: no threshold, but based on previous decisions average of drugs approved is Eur 36,000/QALY, up to Eur 90,000/QALY							
✗	High ICER, likely not acceptable except if exceptional circumstances: - NICE: > £30,000/QALY (e.g. end-of-life treatment) - SMC: no maximum threshold, but accounts for NICE threshold - TLV: no maximum threshold, but based on previous decisions ICER greater than EUR 90,000/QALY							
	*1 SEK = 0.110202 EUR Legend: PAS: Patient Access Scheme; EoL: End-of-Life treatment; severity: disease severity considered high; QALY: quality-adjusted life years; ICER: incremental cost-effectiveness ratio; NICE: National Institute for Health and Care Excellence; SMC: Scottish Medicines Consortium; TLV: Dental and Pharmaceutical Benefits Board; HAS: Haute Autorite de Sante.							

"Other considerations": an overview

125 individual "other considerations" were coded and grouped into 10 categories (Figure 1). These were either provided as background information, by experts, or were considered important for the decision. 94 of these 125 codes were included by NICE and used 173 times across all 10 cases (e.g. one may have been coded for more than one drug), followed by 24 codes used 67 times by HAS, 23 codes used 50 times by SMC, and 33 codes used 56 times by TLV. The most commonly reported disease characteristic related to the nature of the disease, its rarity and unmet need. The most common treatment characteristics related to its type of benefit, innovative nature, indirect benefit or the non-significance of its adverse events.

Figure 1. Proportion of drugs that accounted for a category of "other considerations", per cluster



"Other considerations" as pivotal factors in the decision processes

A proportion of these 125 "other considerations" were also put forward as one of the main reasons for their decisions. These represent 18% of those put forward by NICE (32 of 173), 24% by SMC (12 of 50), 34% by TLV (19 of 56), and 100% by HAS (67 of 67) (Table 3). For the purpose of HAS, these "other considerations" were mainly discussed in the conclusions of the Transparency Committee when assessing the ISP and have all been considered as main reason for the final recommendation.

A proportion of these (e.g. cases with a superscript in Table 3) pertained to those preferences elicited by each HTA body (Table 1), where higher ICERs or uncertain evidence may be accepted. Four drugs were eligible under the NICE end-of-life supplementary advice, three of which were considered cost-effective with an ICER ranging between £34,000-£47,000/QALY (lenalidomide, azacitidine, trabectedin), and the fourth (everolimus) not cost-effective with £51,700/QALY. Weaknesses in the economic model were deemed acceptable because of the SMC modifiers in four cases (eltrombopag, imatinib, azacitidine, lenalidomide). For HAS, all study drugs were recognised as targeting patients with rare diseases and assessed within the framework of one or more ministerial plans. In Sweden, higher ICERs were accepted due to the severity of the conditions.

Cases without a superscript in Table 3 represent the additional (non-quantified or non-elicited) "other considerations" put forward as one of the main reasons for the decision, relating to the scientific and social value judgments made. For NICE, these included the treatment's unmet need for lenalidomide, mifamurtide and mannitol dry, its innovativeness for azacitidine and mifamurtide, and the severity of the disease for mannitol dry.

Additionally, the impact on families' and friends' quality of lives, the rarity of the disease, and the ability to contribute to society and live an active and fulfilling life were also highlighted for mifamurtide. For SMC, these included the oral administration benefit, the orphan status and unmet need (e.g. additional treatment option) for eltrombopag, the potential reduction in resource use for romiplostim, and the life-extending nature of the treatment for mannitol dry and azacitidine. Similarly, TLV also valued certain treatment characteristics, such as its oral administration benefit (e.g. eltrombopag), novel mechanism of action (e.g. eltrombopag, romiplostim), orphan status (e.g. eltrombopag), and the impact of the disease on quality of life and daily activities (e.g. eltrombopag, romiplostim, lenalidomide). Unmet need was also recognised (e.g. eltrombopag, romiplostim), and in one case, TLV acknowledged the changing environment in clinical practice (e.g. lenalidomide). For HAS, both disease and treatment characteristics were put forward for all drugs, namely around the nature of the disease, the need for treatment alternatives, and the direct or indirect benefit from taking the treatment. In France, orphan drugs are presumed to be innovative and thus subject to fast-track HTA consideration. In the assessment, the innovativeness of a drug is recognized for those drugs with ASMR I-III.

Table 3. “Other considerations” as pivotal factors in the decision

	Eltrombopag	Romiplostim	Everolimus	Lenalidomide	Azacitidine	Imatinib	Mannitol dry	Mifamurtide	Ofatumumab	Trabectedin	**Scientific value judgment** *-non-quantified-*	**Social value judgment** *-non-elicited-*
National priority												
- Rare disease plan	HAS[rare]	HAS[rare]			HAS[rare]		HAS[rare]			HAS[rare]		
- Cancer plan			HAS[rare]		HAS[rare]	HAS[rare]		HAS[rare]				
- Plan for improving qol in patients with chronic diseases			HAS[rare]									
- Public Health Law 2004			HAS[rare]	HAS[rare]		HAS[rare]		HAS[rare]				
- Falls in the scope of the fight against cancer	HAS[rare]								HAS[rare]			
Issues around current treatment alternatives												
- changing treatment pathways				TLV							★	
Disease nature affecting the patient												
- Short life expectancy			NICE[end]	NICE[end], HAS	NICE[end], HAS					NICE[end]	★	
- Disease severity	HAS, TLV[severity]	TLV[severity]	TLV[severity]	TLV[severity]			NICE				★	
- Disease with a poor prognosis					HAS						★	
- Serious condition		HAS	HAS				HAS	HAS, TLV[severity]		HAS	★	
- Life threatening	TLV	TLV	HAS	HAS		HAS	HAS	HAS	HAS	HAS	★	
- Incurable				TLV			HAS				★	
- Requires life long treatment	HAS										★	
- Affects quality of life	TLV, HAS	HAS, TLV					HAS				★	
- Affects daily activities and functional capacity	TLV	HAS, TLV									★	
Disease nature affecting the patient's surrounding												
- Impact on quality of life of family and friends								NICE			★	
Rarity, orphan status, small patient population	TLV							NICE				★
- Small patient population			NICE[end]	NICE[end]	NICE[end]		HAS			NICE[end]		
- Minor public health burden because of rarity	HAS	HAS				HAS		HAS		HAS		
- Orphan status	SMC			SMC[modifiers]	SMC[modifiers]	SMC[modifiers]						
Unmet need												★
- Importance of new treatment options							NICE					
- Few developments in last years							NICE	NICE				
- No (satisfactory) alternatives exist	TLV	HAS	HAS			HAS			HAS	HAS		
- Alternatives exist				HAS			HAS	HAS				
- Need to improve therapeutic management									HAS			
- Few therapeutic options	HAS	TLV										
- New treatment would offer new options	SMC											
- Alternative treatments not routinely available				NICE								
Type of treatment benefit												★
- Curative	HAS	HAS, SMC[modifiers]	HAS					NICE[discount], HAS	HAS	HAS		
- Palliative				HAS	HAS							
- Preventive						HAS						
- Symptomatic							HAS					
- Salvage treatment									HAS			
- Life-extending			NICE[end]	NICE[end]	NICE[end],SMC[modifiers]	SMC[modifiers]	SMC	SMC[modifiers]		NICE[end]		
- Benefit extended over a long period								NICE				
Innovative nature of the treatment												★
- Important advance					NICE							
- Novel mechanism of action	HAS	TLV						NICE				
- Significant innovation for a rare disease								NICE				
- New class of drugs	TLV											
- Potential valuable new therapy								NICE				
- Oral administration advantage	TLV, SMC, HAS											
Indirect benefits from taking the treatment								NICE			★	
- Ability to lead an active and fulfulling life								NICE			★	
- Ability to contribute to society					HAS						★	
- Significant impact on morbidity					HAS						★	
- Significant impact on mortality					HAS						★	
- Significant impact on quality of life		HAS, SMC		HAS	HAS						★	
- Resource use reduction												

Legend: end: NICE End-of-life supplementary advice; severity:severe disease; modifiers: SMC modifiers; NICE: National Institute for Health and Care Excellence; SMC: Scottish Medicines Consortium; TLV: Dental and Pharmaceutical Benefits Board; HAS: Haute Autorite de Sante

Stakeholder input

No mention of stakeholder input was found for TLV given that this is done informally and generally not documented. In contrast, formal channels exist to collect stakeholder input during the technology appraisal processes through the Public Involvement Programme (PIP) at NICE, the Patient and Public Involvement Group (PAPIG) at SMC, and the procedures for rapporteurs at HAS. In the latter case, the Transparency Committee meeting minutes note how many outside experts provided input but not the content of their advice.

"Other considerations" were provided by stakeholders in 116 of the 175 identified in the NICE appraisals. 41% of these (n = 116) were provided by clinical experts, 21% by patient representatives, and 35% by both clinical experts and patient representatives. Clinical experts provided information about the nature of the disease affecting the patient (27%), issues around current treatment alternatives (13%), the treatment's unmet need (11%) and innovativeness (10%), and the non-significance of adverse events (10%). Patient representatives provided information about the nature of the disease affecting the patient (33%), the non-significance of adverse events (14%), the indirect benefits from taking the treatment (12%) and the patient's unmet need (11%). In Scotland, all drugs except trabectedin and imatinib received a Patient Interest Group submission. The detail of these submissions was not publicly available. Clinical input was recorded in the reports for two cases, commenting on the treatment pathways in terms of symptoms (e.g.eltrombopag) and unlicensed comparators (e.g romiplostim).

Orphan drugs and special status

Table 4 represents the subcategories of "other considerations" identified in the sampled drugs (rows) and whether they pertain to certain characteristics specific, but not limited to, rare disease and orphan drugs (columns). Unmet need is more likely to characterise rare diseases given the scarcity of relevant knowledge and expertise and the fact that often no effective cure exist. This is due to issues around the diagnosis of some of these rare diseases, the complex and unknown nature of these conditions, together with the lack of coordination amongst centres of expertise at EU- and international-levels, and the lack of knowledge around best practices.(23) Further, given that orphan drugs often do not have effective cure, treatments for rare diseases are more likely to be innovative. On this basis, the "other considerations" that were put forward as one of the main reasons for the final decision identified previously, therefore influencing the final decision, may favour orphan drugs compared to drugs to treat normal conditions. This was seen, for example, with "unmet need" for lenalidomide, mifamurtide and mannitol dry by NICE, and for eltrombopag, romiplostim by SMC.

Table 4. Special status of orphan drugs

	Special status?	**Disease or treatment characteristic specific to rare diseases and orphan drugs**								
Subcategories of "other considerations" (non-quantifiable or non-quantified)	✔specific to orphans ★likely more characteristic of orphans	small patient numbers	scarcity of relevant knowledge and expertise	genetic origin	chronic, progressive, often life-threatening	disabling	no effective cure	75% of rare diseases affect children	30% of rare disease patients die before age of 5	High level of suffering for patient and family
Nature of the disease affecting the patient eg disease severity, impact on quality of life and daily activities	★				✔	✔	✔	✔	✔	✔
Nature of the disease affecting the patients' surrounding eg impact of the disease on the families' quality of lives, anxiety, limiting life choices	★									✔
Rarity, orphan status, small patient numbers	✔	✔								
Unmet need eg no or few treatment alternatives exist, treatment pathway unclear	★		✔				✔			
Type of treatment benefit eg curative, life extending	★						✔	✔	✔	
Innovative nature of the treatment eg new mechanisms of action	★		✔				✔			

Indirect benefit from the treatment eg quality of life improvement, ability to live normal lives, improved symptoms, administration benefit	★				✔	✔		✔	✔	✔
✔Characteristic specific to rare diseases and orphan drugs										
★Characteristics likely specific to rare diseases and orphan drugs										

Discussion

This study identified the value judgments made for ten orphan drugs in four countries in order to understand how they influenced the assessment process. The study also identified cases when these "other considerations" were provided by different stakeholders, by type of information provided, and when they related to rare disease characteristics. Implications are discussed here and focus on five topical areas: (a) the classification framework, (b) existing literature, (c) determinants of social value, (d) accountability for reasonableness, and (e) orphan drugs and special status.

One of the significant contributions of this study is the proposed classification framework of the value judgments bring made during HTA processes (Table 1). It allows to highlight needs for further research (when evidence is incomplete or preferences are non-elicited). If they continue not to be elicited or quantified, retrospectively identifying these to prospectively create a taxonomy of criteria may facilitate their being used more consistently when similar scenarios are encountered in the future. For example, NICE emphasised the impact of osteosarcoma on families' and friends' lives when assessing mifamurtide, or SMC and TLV recognised the "oral administration benefit" when assessing eltrombopag. These are non-quantified or non-elicited criteria for which preference could be given in future cases by their inclusion in the taxonomy of criteria to be accounted for. This is all the more important when considering the extent to which these considerations are different across countries and likely also across decision-making bodies within one HTA agency. These differences are either a consequence of agency-specific value preferences,(24) or of committee-specific preferences

reflecting the composition of the decision panel and their individual judgments driven by their experiences, and it is therefore important to improve the consistency in their use.

The different "other considerations" identified and their classification into sub-categories and clusters are in line with findings from the literature on (social) value judgments. Schwappach (2002) divides the determinants of social value into patient and treatment characteristics.(25) Our study clustered these determinants in a similar manner and takes one step further by applying this same classification to both social and scientific value judgments. Second, a number of individual social values were identified in the literature. One study in England used qualitative techniques to define these, where respondents agreed to favour need, preventive care, quality of life, health improvement and life expectancy, in addition to not favouring certain populations according to age or socio-economic status.(26) Generally there is agreement about what these social values are, but the determinants of social value remain broadly defined and no exhaustive list of these exists. When comparing these results to the topics defined in several of the EUnetHTA Core Model® domains, commonalities and differences are seen.(27) The topics included in the ethical domain relate to societal preferences and the norms or values from using a technology, which corresponds to, in this study, the disease nature affecting patients and their surroundings, and recognised unmet need in terms of how the introduction of a new technology affects the distribution of health care resources. However, the judgment about the magnitude of this unmet need was clearly captured in our results, but does not seem to be explicitly accounted for in the Core Model®. Topics in the social domain relate to the types of resources required and the experiences, actions and reactions from patients when using the technology, and correspond to the elicited societal preferences (e.g. rare diseases), and to the treatment's direct and indirect benefits, including if the adverse events are manageable (e.g. patients' experiences). Topics in the organisational domain relate to the consequences on resources or the organisational aspects

from using the technology, and would correspond to issues with current treatment alternatives or around clinical practice. The innovative nature of the treatment, identified in our study, is captured within the technical characteristics of the technology in the Core Model®, though no explicit definition is provided.(27) The value judgments identified in this study therefore correspond to the different domains included in the Core Model®, and further contribute to understanding their determinants in how they are expressed in practice.

Given that the determinants of social value are only broadly outlined, this study contributes to better defining these. For example, "unmet need" is a determinant of social value. It is accounted for in the weighing of disease severity by TLV, as one of the SMC modifiers, and discussed within NICE Citizen Council meetings. Nevertheless, no clear definition of unmet need exists. Our results captured the variety of ways of expressing "unmet need" (Table 3), which can be used to define it. Another example is disease severity, for which no single definition exists. It is characterised by a number of determinants, which include the impact on quality of life and mobility, or considerations of life expectancy.(8, 28) Severity is included into HTA either through a weighing of the QALY (or of other measures of HTA) or as part of the deliberative process.(8) The latter would apply to our study countries since no specific weighing for severity was seen, including in Sweden where it is explicitly accounted for despite the definition of disease severity being broad (as noted earlier). Our results identified the various forms of expressing severity, which can be used to better define severity for future cases. For TLV, these included: the life-threatening nature of the disease, the negative impact on daily activities including functional capacity and on quality of life, and the short life expectancy from having the disease. In France, where no ICER or threshold exist, informal methods are used to incorporate societal and political values into the assessments. This is explicit in the evaluation of the public health value (intérêt de santé publique) of drugs

as part of the coverage evaluation (SMR), however, whether these determinants of (social) value are accounted consistently across cases is another question, which could be partly addressed by applying the taxonomy of criteria.

For a resource allocation decision to be accountable for reasonableness, the process should be transparent and public, based on reasons that are relevant, decisions should be revisable when new evidence is available, and the process should allow for these conditions to be enforced.(9, 29) This usually takes place during the deliberative process of HTA, during which the Committee discusses the evidence and accounts for stakeholder opinion until a decision is made. The decision and reasons for the decision should then be documented in the HTA report, most often publicly available, as is the case with our study countries. In terms of stakeholder input, a clear process exists at NICE and SMC where they are given the opportunity to voice their concerns or opinions. Our analysis confirmed that this is well-reported for NICE (given the high number of "other considerations" provided by different experts), but is not as detailed in SMC's summary of advice, probably because it is a less detailed report. HAS has specific procedures governing outside experts (rapporteurs) who provide advice and input in the evaluation process. For TLV, no official procedures exist, although some of the key stakeholders are represented within the Appraisal Committees (e.g. clinical experts). Generally, the type of input from these stakeholders could be better documented or transparent. Some argue that it is not sufficient to have a formal procedure to account for stakeholder input and value judgments, but that it should also be clear how these have influenced the decision, which is often lacking.(8) Our results further confirm this in the number of "other considerations" (from stakeholders or not) identified, where it is not entirely clear how these factors contributed to the decisions particularly in those cases where these were (non-elicited or non-quantified) value judgments. The taxonomy of criteria developed together with the type of input from different stakeholders may help understand

the criteria that are relevant to decision-making and their sources that go beyond routine methods of assessing clinical benefit and ICERs.

Little agreement exists on whether patients with rare diseases requiring orphan drug treatments deserve a preferential status.(13-15) Nevertheless, governments recognise the difficulties in appraising these treatments and the fact that they should be treated differently. In France, patients with orphan diseases have a preferential status, but their needs go beyond drugs. Only recently, NICE and SMC have implemented new procedures for end-of-life and ultra-orphan drugs. The treatment's additional benefit and other elements not captured by the ICER (e.g. unmet need, disease severity, added value the patient and surrounding) are now accounted for by SMC, together with patient and clinical engagement. These other elements correspond to the "other considerations" identified in this study. Similar questions are arising in Sweden, where a consultation on how to appraise orphan drugs has recently been issued. Further, in NICE's recent consultation on value-based pricing, they attempted to find novel approaches to capturing burden of illness and other issues. They concluded that approaches to adjusting the QALY were insufficient, whereby explicitly accounting for these additional criteria is essential for decision-making. This study provides an alternative to the issue of preferential status by accounting for the non-elicited or non-quantified "other considerations" that influenced previous decisions, and query whether it would be worth eliciting preferences for these. This could then feed into novel approaches in assessing orphan drugs (e.g. MCDA).

Conclusions

This study systematically identified the scientific and social value judgments made in four countries for a sample of orphan drugs, and explored how they influenced the deliberative

process of HTA. The proposed classification framework of these value judgments was used to identify needs for further research and to improve consistency in their use across cases. This was then used to address different issues around identifying and better defining the determinants of social value or how to improve the lack of accountability for reasonableness particularly in cases when it was not clear how the "other considerations" identified influenced the decisions. It also provided a way forward to eliciting whether these orphan drugs deserve a special status by eliciting preferences around some of the social value judgments made which are more likely to pertain to orphan compared to non-orphan drugs, rather than focusing on the opportunity cost of these. Given the challenges in producing robust evidence for orphan drugs due to the small patient numbers and heterogeneity of the diseases, scientific and social value judgments are unavoidably part of the decision processes for these drugs. Their identification through the application of this framework enables us to create a taxonomy of criteria relevant to these decision-making processes, which go beyond routine methods for HTA.

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