

EXPLORING VALUES OF HEALTH TECHNOLOGY ASSESSMENT AGENCIES USING REFLECTIVE MULTICRITERIA AND RARE DISEASE CASE

Mireille M. Goetghebeur

LASER

School of Public Health, University of Montreal

mm.goetghebeur@umontreal.ca

Monika Wagner

Dima Samaha

William O'Neil

Danielle Badgley

LASER

Hector Castro-Jaramillo

Ministry of Health, Colombia

Payam Abrishami

National Health Care Institute ZINL

Antonio Sarria-Santamera

Agencia de Evaluación de Tecnologías Sanitarias (AETS) of Instituto de Salud Carlos III, Faculty of Medicine, University of Alcalá

Irina Cleemput

Belgian Health Care Knowledge Centre (KCE)

Michele Tringali

Lombardia Health Directorate

Objectives: Tackling ethical dilemmas faced by reimbursement decision makers requires deeper understanding of values on which health technology assessment (HTA) agencies are founded and how trade-offs are made. This was explored in this study including the case of rare disease.

Methods: Representatives from eight HTA explored values on which institutions are founded using a narrative approach and reflective multicriteria (developed from EVIDEM, criteria derived from ethical imperatives of health care). Trade-offs between criteria and the impact of incorporating defined priorities (including for rare diseases) were explored through a quantitative values elicitation exercise.

Results: Participants reported a diversity of substantive and procedural values with a common emphasis on scientific excellence, stakeholder involvement, independence, and transparency. Examining the ethical imperatives behind EVIDEM criteria was found to be useful to further explore substantive values. Most criteria were deemed to reflect institutions' values, while 70 percent of the criteria were reported by at least half of participants to be considered formally by their institutions. The quantitative values elicitation highlighted the difficulty to balance imperatives of "alleviating or preventing patient suffering," "serving the whole population equitably," "upholding healthcare system sustainability," and "making decisions informed by evidence and context" but may help share the ethical reasoning behind decisions. Incorporating "Priorities" (including for rare diseases) helped reveal trade-offs from other criteria and their underlying ethical imperatives.

Conclusions: Reflective multicriteria are useful to explore substantive values of HTAs, reflect how these values and their ethical underpinnings can be operationalized into criteria, and explore the ethical reasoning at the heart of the healthcare debate.

Keywords: HTA, Values, Ethics, Reflective Multicriteria, Rare disease

Healthcare systems are challenged by the tension between delivering quality care and best treatments to individual patients, serving equitably the entire population covered, and maintaining sustainability (1). Berwick et al. (2) proposed that high-value health care will be achieved only if stakeholders pursue a broad system of linked goals related to individual patient health, population health, and healthcare system resource

management, referred to as the triple aim. Coverage decision makers frequently face ethical dilemmas as how to represent these apparently conflicting aims in the decisions being made. Reflecting on the extent to which diverse values are represented and traded-off is critical in making accountable and legitimate decisions. Current health technology assessment (HTA) methodologies are constantly challenged to address these issues, as exemplified by the controversy around treatments with acceptable cost-effectiveness ratios that are nevertheless challenging sustainability, such as recent treatments for hepatitis C (3), and issues raised by therapies for rare diseases, which require consideration of aspects usually not formally addressed by current HTA approaches (4;5).

We thank Mirella Marlow from NICE, United Kingdom; Bjorn Hofmann from the University of Oslo, Norway; and Ken Bond from the Canadian Agency for Drugs and Technologies in Health (CADTH), Canada, for their participation in the study and their insightful contributions. The study was funded by a small consortium with financial contributions from Genzyme (United States), Radboud University (Netherlands), and the EVIDEM Collaboration.

HTA agencies are founded on and make coverage decision making amidst diverse social values (6), including substantive values (e.g., fairness), embedded in the evaluation criteria, and procedural values (e.g., transparency, accountability and participation) embedded in the evaluation process (7;8). Several have argued for an expanded HTA that goes beyond safety, efficacy, and cost-effectiveness to include elements such as equity, budget impact, and financial protection, embedded in a fair and evidence-based deliberative process that ensures consideration of diverse stakeholder perspectives and meets the conditions for accountability for reasonableness (A4R) (9–11).

Hofmann et al. (12) stressed the need to acknowledge that value judgments and their diversity are inherent in HTA. Accountability also requires tackling ethical dilemmas in a fair manner, but, although there is a level of agreement on the basic principles for priority setting, as Daniels and van der Wilt (6) pointed out, there is no agreement on how to trade-off between competing goals such as population health maximization and fairness. Building on these premises, we propose that resolving the tension faced by decision makers requires further exploration of substantive values on which HTA agencies are founded and of ethical trade-offs inherent to decisions. The objective of this study is to perform this exploration using a narrative approach and reflective multicriteria as a means to foster a culture of pragmatic complexity in an inclusive and deliberative manner to further reasonableness and accountability.

METHODS

Questionnaire

A questionnaire was designed to collect feedback on the mandates and values of HTA agencies, examine ethical underpinnings of the values on which these agencies are founded, and explore trade-offs. EVIDEM was selected as a reflective multicriteria framework to facilitate this process. It contains twenty generic criteria that are explicitly rooted in the key ethical imperatives underlying healthcare decisions: (i) the imperative to prevent or alleviate patient suffering (an aspect of deontology); (ii) the imperative to serve the whole population equitably, which suggests helping first those who are worst off (an aspect of distributive justice, fairness), while providing healthcare to the greatest number (an aspect of utilitarianism); (iii) the imperative to uphold healthcare system sustainability (an aspect of utilitarianism), and (iv) the imperative to make decision informed by relevant evidence and the specific context (an aspect of practical wisdom) (4;13;14). (It is acknowledged that in addition to the ones stated, other ethical theories could be summoned to underpin these imperatives.) For the thirteen normative, non-context-specific criteria of the framework, there is universal agreement on the scoring direction (e.g., provided everything else is the same, it is better to have high efficacy, to avoid adverse events, to target the most severe diseases etc.),

which makes it possible to design scoring scales that allow assessing an intervention against these criteria in a quantitative manner. (Of note, the term “quantitative assessment” here means eliciting scores that represent interpretations and judgments on the evidence rather than a numerical transformation of the evidence.) For the remaining seven criteria, scoring directions would need to be determined in specific contexts; these are, therefore, assessed qualitatively in the generic framework.

The first part of the questionnaire followed a narrative approach, through which participants provided written statements describing (i) the mandate, (ii) the mission, (iii) the motto, (iv) the social values (substantive and procedural) guiding each agency’s process.

The second part followed a reflective multicriteria approach derived from EVIDEM, during which participants were presented with the underlying ethical aspects, methodological justification (nonredundant, independent, operationalizable and complete) and definition of each criterion, and then asked: (a) to explore whether it reflected the values of their institution, (b) whether it was formally considered in their process and (c) provide verbal or written comments through a guided discussion.

In the third part, the quantitative values elicitation exercise, participants explored trade-offs between the quantitatively assessed criteria of EVIDEM (along with their ethical underpinnings) by distributing weighting points across domains and criteria (hierarchical point allocation), as shown in Figure 1. Participants also shared their thoughts on whether such exercise would be helpful to support their individual reflection regarding trade-offs and share their perspectives with others. (Of note, the numbers generated should not be considered as conventional numbers but as a representation of individual reflections.)

The fourth part of the questionnaire was designed to investigate issues and ethical dilemmas pertaining to appraising interventions for rare diseases. It provided a list of rare disease issues, identified from a systematic review (4) and categorized by criteria, and prompted participants to indicate additional issues. To explore trade-offs inherent in appraising interventions for rare diseases, participants repeated the quantitative values elicitation exercise with *Population priorities* (split into criteria *Rare diseases* and *Other priorities*) added as an additional trade-off domain (Figure 1) (4).

Workshop Design

We contacted representatives of ten national HTA agencies, based on their interest in values, ethics and multicriteria approaches, to participate in a 1-day face-to-face workshop in Oslo, Norway, in 2015. Participants received the questionnaire before the workshop and completed the first part (narrative approach) individually. During the workshop, participants were introduced to the ethical and methodological principles that underpin the framework and were guided to complete the

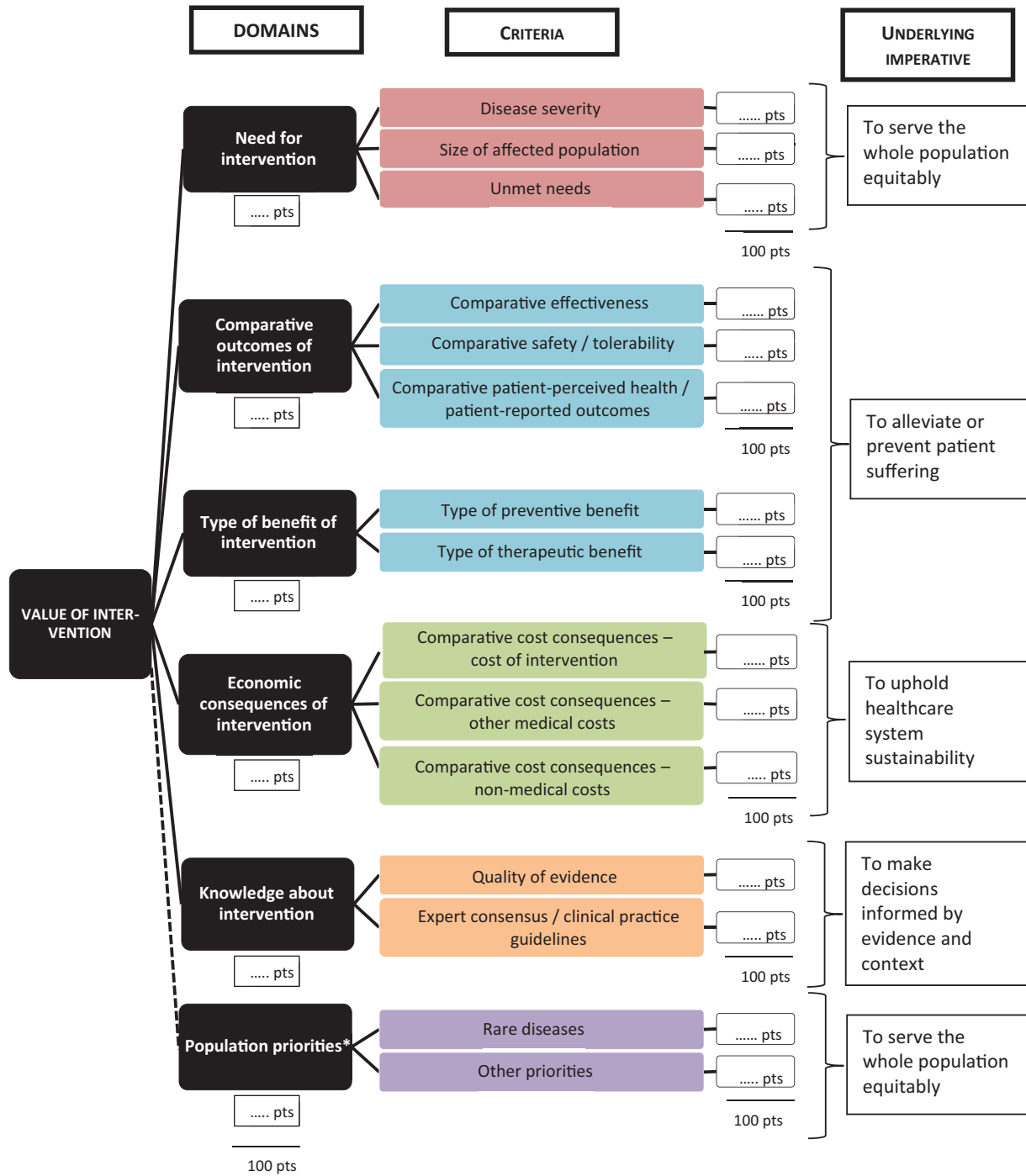


Figure 1. Hierarchical point allocation exercise for values elicitation and exploration of trade-offs between criteria along with their key ethical imperatives.

other parts of the questionnaire. Each part was followed by a structured discussion. The workshop was conducted under the Chatham House Rule to facilitate open exchange.

Data Analyses

All responses from the questionnaires and the discussion were collected, analyzed, and structured in tabular format. Criteria weights collected were analyzed and compared using descriptive statistics. Weights assigned with and without the *Population priorities* criterion included in the quantitative criteria set

were compared to identify where trade-offs related to defined priorities, including for rare diseases, were made. Cumulative weights for clusters of criteria representing key ethical imperatives were also calculated.

RESULTS

Organizations and Participants

Eight participants attended the workshop, each representing one HTA agency: the Belgian Health Care Knowledge Centre

(KCE); the Canadian Agency for Drugs and Technologies in Health (CADTH); the Health Technology Assessment Institute (IETS) Colombia; the National Institute for Health and Care Excellence (NICE) UK; the Lombardy Region Health Directorate, Italy; the National Health Care Institute (ZIN) Netherlands; the Norwegian Knowledge Centre for the Health Services (NOKC); and the Instituto de Salud Carlos III, Spain.

Narrative Approach: Mandates, Missions, Mottos and Values of Agencies

Participant statements on the mandates, missions, mottos and values of their agencies expressed a diversity of values (Table 1). Participants represented organizations with the mandate to provide guidance and recommendations to national or regional decision makers. Examination of these statements indicates that, overall, participating agencies aim at promoting the use of impartial evidence in decision making to serve the greater purpose of providing quality care to the population and optimal use of healthcare technology. Many of the various terms provide reflected the key ethical imperatives introduced above, including the imperative to prevent or alleviate patient suffering (reflected in terms such as *Improve patient care*, *Improve patient safety*, *Clinical benefit*, *Focus on patients*); to serve the whole population equitably (*Equitable*, *Distributive justice*, *Need*), to uphold healthcare system sustainability (*Efficiency*, *Resource stewardship*, *Sensible care*), and to make decisions informed by relevant evidence and the specific context (*Evidence-based*, *Scientific rigor*, *Scientific excellence and quality*). Exploration of procedural values of the organizations reveals a common emphasis on stakeholder involvement/collaboration, independence and transparency.

Reflective Multicriteria Approach: Criteria, Ethics, Institutional Values, and Rare Disease Specificities

Participants reported on whether and how each criterion, and its underpinning ethical imperative, reflected the values of their organization and whether it is formally considered in their processes (Table 2). Specific issues reported for rare diseases are also included. Exploring the ethical aspects underpinning the criteria was deemed by participants a useful approach to explore institutional values. Ninety percent of the EVIDEM criteria were thought by at least half of the participants to reflect their institutions' values, while 70 percent of the criteria were reported by at least half to be considered formally by their institutions.

Criteria Representing the Imperative to Prevent or Alleviate Patient Suffering. The criterion *Comparative effectiveness*, rooted in the imperative to alleviate/prevent suffering to the greatest extent, was reported by all participants to reflect their institutions' values and considered in their processes. It was regarded as a dominant criterion, considered extensively in particular with regard to an efficient use of resources, if opportunity cost is sizeable. It was pointed out that high societal expectations related to the ben-

efits of rare disease treatments have to be balanced by careful consideration of meaningful outcomes of effectiveness.

Expressing the call to *do no harm* at the patient level, *Comparative safety/tolerability* was reported to reflect all participating institutions' values and to be formally considered by 75 percent of them. A key criterion alongside effectiveness, considering safety and tolerability was deemed essential to the provision of quality care. Participants pointed out that, unlike regulatory assessment, the HTA process considers the impact of adverse events assuming safety in a regulatory sense to be already established.

Comparative PROs was reported by 75 percent of the respondents to reflect their institutions' values and by 50 percent to be formally considered. Participants commented that the purpose of this criterion is to take into account patients' expectations and ethical aspects, in response to the call to respect patients' autonomy and dignity. However, participants also pointed out that data derived directly from patients, which would be needed to adequately operationalize this criterion, are frequently lacking. Indeed, although noted in the narrative approach as a key substantive value, integration of the patient perspective in the decision-making process remains challenging.

Criteria *Type of preventive benefit* and *Type of therapeutic benefit* are rooted in the imperative to eliminate suffering rather than merely alleviate it, either through prevention or cure, respectively. For both of these criteria, 88 percent of participants reported that they reflected their institutions' values. However, preventive strategies are frequently appraised in separate processes or other agencies, and 38 percent of participants reported that this criterion is not formally considered in their HTA process. The concept of *type of benefit*, as opposed to *extent of benefit* assessed under the criterion *Comparative effectiveness*, was considered to pertain to the notion of maximizing the performance of the healthcare system by aiming toward the most relevant type of benefit. In France, this is made explicit through the concept *type of medical service* (Service Medical Rendu) used by the Haute Autorité de Santé.

Criteria Representing the Imperative to Serve the Whole Population Equitably. *Disease severity*, a criterion rooted in the imperative to prioritize those who are suffering or might suffer the most, was reported by 88 percent of participants to reflect their institutional values and to be used formally in their processes. Participants reported disease severity as "a major criterion" and "an essential component." However, the concept of *Disease severity* was also questioned on the basis that a condition's natural course may be less important than its course under current treatments. The latter relates to the concept of *unmet needs for a given condition*, which is a separate criterion rooted in distributive justice with the aim of prioritizing populations who have limited alternatives.

Table 1. Mandates, Missions, Mottos Values and Ethical Foundations of Agencies

Agency	Mandate and mission	Motto	Social values and ethical foundations
Belgian Health Care Knowledge Centre (Federaal Kenniscentrum voor de Gezondheidszorg - Centre fédéral d'Expertise des soins de santé, KCE)	<p>To produce independent evidence-based advice to policy makers to allow them taking efficient resource allocation decisions to ensure that healthcare provided is of the best quality and as accessible as possible to patients. This is done by:</p> <ul style="list-style-type: none"> • Evaluating medical technologies and medicinal products in HTA, • Investigating the optimal means of organising and funding health care (Health Services Research), and • Developing effective methods for supporting evidence-based policy making <p>To give guidance to healthcare providers through the development of good clinical practice guidelines (GCP)</p>	Supporting evidence-based decision making in healthcare aiming at high quality, efficiency and accessibility in the healthcare system	<p>Substantive values:</p> <ul style="list-style-type: none"> • Scientific excellence and quality • Performance, accessibility, quality and safety of healthcare • Focus on patients <p>Procedural values:</p> <ul style="list-style-type: none"> • Independence and objectivity • Multidisciplinarity • Transparency of research processes • Stakeholder involvement (patients, policy makers, clinicians, etc.) • Deontology (conflict of interest policy) • Dynamic communication • Good governance
Canadian Agency for Drugs and Technologies in Health (CADTH)	<ul style="list-style-type: none"> • To provide decision makers in the healthcare system with credible, impartial evidence about health technologies and make recommendations regarding appropriate and optimal use. • CADTH does not make policy decisions, nor are the recommendations of its expert committees (CDEC, pERC, HTERP) binding • To enhance the health of Canadians by promoting the optimal use of health technologies 	Evidence driven	<p>The responses below reflect the values and principles for the assessment and appraisal of medical devices, procedures and diagnostics HTA and Optimal Use Program and the appraisal committee the Health Technology Expert Review Panel.</p> <p>Substantive values:</p> <ul style="list-style-type: none"> • Organizational values: leadership, excellence, responsiveness, collaboration • Values pertaining to HTA work: relevance • Decision framework values for HTERP: Need, clinical benefit, harms, patient preferences, cost-effectiveness and budget impact, ethical issues, legal and social issues, implementation issues, environmental issues, other issues. <p>Procedural values:</p> <ul style="list-style-type: none"> • No procedural values are stated explicitly; however, transparency is a predominant value in the activities of HTERP

Table 1. Continued

Agency	Mandate and mission	Motto	Social values and ethical foundations
Colombia: Institute of Health Technology Assessment (<i>Instituto de Evaluación Tecnológica en Salud, IETS</i>)	<ul style="list-style-type: none"> To conduct HTAs and support the development of CPGs to better inform decision makers in Colombia. In 2016, IETS will be recognized by the Colombian society, the government and the scientific and academic community, as the main reference and coordinating body of the processes of HTA and CPG development, aimed at informing decisions in healthcare. IETS will also be leader in the region, promoting use of evidence to inform decision making in health, in a technically rigorous, independent and <i>participatory</i> manner. To contribute to the development of better public policies and healthcare practice, through HTAs and CPGs, technically rigorous, independent and participative 	Evidence promoting trust	Substantive values: <ul style="list-style-type: none"> Robustness Independence Stakeholder engagement (related to content of processes -key criteria/aspects considered) Procedural values: <ul style="list-style-type: none"> Transparency Independence Accountability
England and devolved nations: National Institute for Health and Care Excellence (NICE)	<p>To improve outcomes for people using the National Health Service and other public health and social care services. We do this by:</p> <ul style="list-style-type: none"> Producing evidence-based guidance and advice for health, public health and social care practitioners. Developing quality standards and performance metrics for those providing and commissioning health, public health and social care services. Providing a range of information services for commissioners, practitioners and managers across the spectrum of health and social care 	Improving the quality of care through careful and targeted use of finite resources	Substantive values: <ul style="list-style-type: none"> Moral principles of respect for autonomy, non-maleficence, beneficence and distributive justice delivered through Social Value Judgement principles Procedural values: <ul style="list-style-type: none"> Autonomous, independent public body Procedural justice by means of ‘accountability for reasonableness’ delivered through scientific rigour, inclusiveness, transparency, independence, challenge, review, support for implementation, timeliness
Italy: Lombardy Region General Health Directorate (<i>Direzione Generale Sanità di Regione Lombardia</i>)	<p>Evaluate the appropriateness of the use of drugs, medical devices and diagnostic and therapeutic technologies as part of the Regional Health Service and make decisions based on the evaluation.</p>	Not stated	Substantive values: <ul style="list-style-type: none"> Consider an extensive list of element of knowledge Multicriteria decision analysis including a wide range of criteria Rigorous evidence for each criteria Procedural values: <ul style="list-style-type: none"> Transparency Independence Appropriateness Conflict of interest policy Communication

Table 1. Continued

Agency	Mandate and mission	Motto	Social values and ethical foundations
<p>Netherlands: National Health Care Institute (<i>Zorginstituut Nederland</i>, ZIN)</p>	<p>ZIN is involved in two Dutch statutory health insurance schemes: the Health Insurance Act (<i>Zorgverzekeringswet</i>) and the Long-term Care Act (<i>Wet Langdurige Zorg</i>). ZIN has an important role in maintaining the quality, accessibility and affordability (financial sustainability) of health care in the Netherlands. This involves:</p> <ul style="list-style-type: none"> • managing the basic healthcare package; • encouraging improvements in healthcare quality; • advising on innovations in healthcare professions and education; and • implementing risk adjustment among insurers. <p>Mission: ZIN advises on access to good-quality insured care, no more and no less than necessary!</p>	<p>Taking care of good health care</p>	<p>Substantive values:</p> <ul style="list-style-type: none"> • Reliance on utmost state of knowledge • Legitimising decisions: Taking into account a host of patient-related and societal aspects in decision making • Supporting patients to make decision • Maintaining social solidarity derived from universal coverage • Maintaining citizens' willingness to pay premium by ensuring that value for money is generated. <p>Procedural values:</p> <ul style="list-style-type: none"> • Transparency • Contact with all stakeholders • Independent organisation in the Dutch healthcare system: in between politics and citizens • Multidisciplinary teamwork • Hosting external advisory committees • Initiative taking • Conflict of interest policy
<p>Norwegian Knowledge Centre for the Health Services (NOKC)</p>	<ul style="list-style-type: none"> • NOKC contributes to quality improvement in the health services by summarising research, promoting the use of research results, measuring the quality of health services, and working to improve patient safety 	<ul style="list-style-type: none"> • Not stated 	<p>Substantive values:</p> <ul style="list-style-type: none"> • Quality • Safety <p>Procedural values:</p> <ul style="list-style-type: none"> • Transparency • Openness
<p>Spain: Agencia de Evaluación de Tecnologías Sanitarias (AETS) of the Instituto de Salud Carlos III (ISCIII)</p>	<ul style="list-style-type: none"> • To ensure equity and improve the efficiency of the National Health System facilitating the decision making regarding the inclusion and exclusion of benefits, changing the conditions of use, increasing the quality and reducing the variability in clinical practice through the production of assessment and evaluation reports and clinical practice guidelines through the synthesis of rigorous scientific information. • To produce scientific advice regarding the introduction and use of healthcare technologies in the Spanish National Health System (NHS) through: <ul style="list-style-type: none"> • Ensuring a common methodological framework of quality in the assessment and development of the work; • Managing and coordinating the preparation of reports of health technology assessment; and • Collaborating in the identification and prioritization of needs and opportunities in health technology assessment. 	<ul style="list-style-type: none"> • Not stated 	<p>Substantive values:</p> <ul style="list-style-type: none"> • Safety • Effectiveness • Quality • Equity • Efficiency <p>Procedural values:</p> <ul style="list-style-type: none"> • Coherent with the priorities of the National Health System • Rigor and soundness • Independence • Transparency • Collaboration

Table 2. Decision Criteria and Ethical Underpinnings: Participants' Insights on Their Relation with Institutional Values, Appraisal Processes and Rare Disease Specificities

Criteria Definition, possible sub-criteria <i>Ethical foundation</i>	Participants' input
<p>Criteria representing the imperative to prevent or alleviate patient suffering</p> <p>Comparative effectiveness Capacity of the proposed intervention to prevent or to produce a desired (beneficial) change in signs, symptoms or course of the targeted condition above and beyond beneficial changes produced by alternative interventions. Includes efficacy and effectiveness data, as available <u>Possible sub-criteria:</u> Magnitude of health gain; percentage of the target population expected to achieve the anticipated health gain; onset and duration of health gain; type of outcomes (specific to therapeutic area) <i>Alleviate suffering to the greatest extent</i></p>	<p><i>Reflects your institution's values (% yes): 100%</i> <i>Formally considered in appraisal process (% yes): 100%</i> <i>Sub-criteria specified:</i> specific disease outcomes, life years gained, quality-adjusted life years gained <i>General comments:</i></p> <ul style="list-style-type: none"> • A "dominant criteria for both assessment and appraisal". • This criterion is probably considered more extensively given the (relative) amount of information available. • The criteria is perceived by many as a reflection of the efficient use of resources in a context where "opportunity costs are relevant" • Selection of the comparator may be a challenge <p><i>Rare disease specificities:</i></p> <ul style="list-style-type: none"> • Limitations with respect to clinical outcome validation (i.e., issue of surrogate outcomes) and definition of meaningful improvement • There are high societal expectations associated with rare disease therapies: it is important to critically appraise claims pertaining to the type and extent of clinical outcomes • Benefit profile needs to be evaluated for all treatments, including those for rare diseases • Providing evidence that the therapy meets a real unmet need (i.e., a meaningful outcome) is crucial
<p>Comparative safety/tolerability Capacity of the proposed intervention to produce a reduction in intervention-related harmful or undesired health effects compared to alternative interventions <u>Possible sub-criteria:</u> adverse events; serious adverse events; fatal adverse events; short-term safety; long-term safety; tolerability <i>Hippocratic Oath: "Do no harm"</i></p>	<p><i>Reflects your institution's values (% yes): 100%</i> <i>Formally considered in appraisal process (% yes): 75%</i> <i>Sub-criteria specified:</i> adverse events; serious adverse events; fatal adverse events; short-term safety, risk compared to the risk of alternatives <i>General comments:</i></p> <ul style="list-style-type: none"> • This criterion is essential to the provision of quality care and is technology dependent. • This criterion is key alongside efficacy/effectiveness during both assessment and appraisal • Adverse events are considered in the HTA process whereas safety of pharmaceuticals in the regulatory sense is deemed established and, therefore, is not considered. <p><i>Rare disease specificities: Not stated</i></p>
<p>Comparative patient-perceived health/patient-reported outcomes Capacity of the proposed intervention to produce beneficial changes in patient-perceived health and patient-reported outcomes (e.g., quality of life) above and beyond beneficial changes produced by alternative interventions; also includes improvement in convenience to patients <u>Possible sub-criteria:</u> improvement in health-related quality of life; impact on autonomy; on dignity; convenience/ease of use/mode & setting of administration <i>Alleviate suffering as perceived by the patient (Hippocratic Oath: "For the good of my patient")</i></p>	<p><i>Reflects your institution's values (% yes): 75%</i> <i>Formally considered in appraisal process (% yes): 50%</i> <i>Sub-criteria specified:</i> health-related quality of life, autonomy, dignity, ease of use, patient preferences, acceptability of the health technology <i>General comments:</i></p> <ul style="list-style-type: none"> • This criteria reflects the value of beneficence and a patient-centered approach and ensures that their expectations and ethical aspects are considered • The relevant outcomes are usually extracted from the evidence or clinicians consensus, but rarely from patients' data. • <i>Rare disease specificities: Not stated</i>
<p>Type of preventive benefit Disease risk reduction provided by the proposed intervention at the population-level (e.g., prevention, reduction in disease transmission, reduction in the prevalence of risk factors). Public health perspective.</p>	<p><i>Reflects your institution's values (% yes): 88%</i> <i>Formally considered in appraisal process (% yes): 38%</i> <i>Sub-criteria specified:</i> prevention of addictions, screening programs, integrated prevention strategies for children and chronic diseases, disease risk reduction at a population level, social interventions</p>

Table 2. Continued

Criteria Definition, possible sub-criteria <i>Ethical foundation</i>	Participants' input
<p>Possible sub-criteria: NA</p> <p><i>Protect health and prevent suffering</i></p>	<p><i>General comments:</i></p> <ul style="list-style-type: none"> From an appraisal perspective, the efficacy of a preventive intervention is considered with the same lens as a curative one. One participant noted that public health interventions often do not follow the same decision-making pathway (i.e., different governmental bodies) as individual coverage interventions and, therefore, may not be considered in the same way. <p><i>Rare disease specificities: Not stated</i></p> <p><i>Reflects your institution's values (% yes): 88%</i></p> <p><i>Formally considered in appraisal process (% yes): 63%</i></p>
<p>Type of therapeutic benefit</p> <p>Nature of the clinical benefit provided by the proposed intervention at the patient-level (e.g., symptom relief, prolonging life, cure).</p> <p>Possible sub-criteria: NA</p> <p><i>Aim to eliminate rather than merely alleviate suffering</i></p>	<p><i>General comments:</i></p> <ul style="list-style-type: none"> This criterion reflects how significant are the health benefit The criterion is considered as part of the appraisal process when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health. It could be reflected as a higher life expectancy and higher health-related quality of life and, therefore, be part of the performance of the healthcare system. <p><i>Rare disease specificities:</i></p> <ul style="list-style-type: none"> There are high societal expectations associated with rare disease therapies: it is important to critically appraise claims pertaining to the type and extent of clinical outcomes
<p>Criteria representing the imperative to serve the whole population equitably</p> <p>Disease severity</p> <p>Severity of the health condition of patients treated with the proposed intervention [or of the health condition that is to be prevented] with respect to mortality, morbidity, disability, function, impact on quality of life, clinical course (i.e., acuteness, clinical stages)</p> <p>Possible sub-criteria: Effect of disease on life-expectancy; on morbidity (includes disability and function); on patients' quality of life; on caregivers' quality of life</p> <p><i>Alleviate suffering in those who are worst off</i></p>	<p><i>Reflects your institution's values (% yes): 88%</i></p> <p><i>Formally considered in appraisal process (% yes): 88%</i></p> <p><i>Sub-criteria specified:</i> effect of disease on morbidity (includes disability and function); effect of disease on patients' quality of life; disease risk factors; natural course of the disease; burden of the disease.</p> <p><i>General comments:</i></p> <ul style="list-style-type: none"> Respondents highlighted the importance of this criterion in their appraisal/assessment process ("a major criterion in appraising interventions", "an essential component of any HTA report", "for priority setting in resource allocation") Severity of the disease <i>per se</i> (i.e., its natural course if not treated) may be less important than the "therapeutic need" (i.e., severity of the disease in the context of current treatments) <p><i>Rare disease specificities:</i></p> <ul style="list-style-type: none"> Rare diseases often have impact on all aspects of life expectancy, quality of life and disability
<p>Unmet needs</p> <p>Shortcomings of comparative interventions in their ability to prevent, cure, or ameliorate the condition targeted; also includes shortcomings with respect to safety, patient-reported outcomes and convenience.</p> <p>Possible sub-criteria: Unmet needs in efficacy; in safety; in patient-reported outcomes; Patient demand</p> <p><i>Alleviate suffering in individuals with limited alternative interventions</i></p>	<p><i>Reflects your institution's values (% yes): 100%</i></p> <p><i>Formally considered in appraisal process (% yes): 75%^a</i></p> <p><i>Sub-criteria specified:</i> availability of alternatives, "shortcomings of current treatment of care"</p> <p><i>General comments:</i></p> <ul style="list-style-type: none"> This criteria reflects the quality of care that should be pursued by the healthcare system One respondent considers that while unmet need is a criteria for the topic selection, it is "less important in the appraisal process" <p><i>Rare disease specificities:</i></p> <ul style="list-style-type: none"> Few therapies, limited clinical expertise, health services not adapted Lack of treatment alternatives for a highly severe disease (often the case for rare diseases) was noted as a strong argument in favor of coverage One participant reported that consideration for unmet need has been formalized explicitly for patients with rare disease

Table 2. Continued

Criteria Definition, possible sub-criteria <i>Ethical foundation</i>	Participants' input
<p>Size of affected population (Number of people affected by the condition (treated or prevented by the proposed intervention) among a specified population at a specified time; can be expressed as annual number of new cases (annual incidence) and/or proportion of the population affected at a certain point in time (prevalence). <u>Possible sub-criteria:</u> prevalence, incidence <i>Alleviate suffering in as many individuals as possible</i></p>	<p><i>Reflects your institution's values (% yes): 63%</i> <i>Formally considered in appraisal process (% yes): 88%</i> <i>Sub-criteria specified:</i> prevalence, incidence <i>General comments:</i></p> <ul style="list-style-type: none"> • This criterion was considered particularly relevant with regards to the assessment of the efficient use of healthcare resources (e.g., size of budget impact), although it may not be explicitly included in an institution's mandate / values or established process. • This criteria is important with regards to the prioritization of research topics • "Although the consideration of this criteria may contribute to the high value of an intervention for common severe diseases; rarity of a condition is not an indicator of low value of an intervention" <p><i>Rare disease specificities:</i></p> <ul style="list-style-type: none"> • Although individually small in number, all rare diseases combined amount to a very significant size of population • Individual patients' 'right to access' to beneficial therapies is much stronger than limited size of affected population
<p>Population priorities and access Alignment of the intervention with current priorities of health system/plan. Priorities for specific groups of patients are defined by societies/decision makers and reflect their moral values. Such considerations are aligned with the principle of fairness, which considers treating like cases alike and different cases differently and often gives priority to those who are worst-off. <u>Possible sub-criteria:</u> Current priorities of health system (e.g., disabled; low-socioeconomic status; specific age groups); special populations (e.g., ethnicity); remote communities; rare diseases; specific therapeutic areas <i>Principle of fairness</i></p>	<p><i>Reflects your institution's values (% yes): 88%</i> <i>Formally considered in appraisal process (% yes): 38%</i> <i>General comments:</i></p> <ul style="list-style-type: none"> • "Consideration of ethical issues, including equitable distribution among vulnerable groups is a core deliberative criterion" • One participant noted that this criteria was important in the topic selection part, however, the criteria is not accounted for in a different manner in the appraisal process <p><i>Rare disease specificities:</i></p> <ul style="list-style-type: none"> • In some setting, special consideration or special approaches are given to rare diseases • Regulatory (and other) policies reflect prioritization status (e.g., orphan designation) • Is the property of being rare a disease property that changes radically the need to interpret needs and solutions according to (contextual but consistent) value-based metrics shaped by general purpose criteria?
<p>Criteria representing the imperative to uphold sustainability of healthcare systems</p>	
<p>Comparative cost consequences – cost of intervention Net cost of covering the intervention. This represents the differential between expected expenditure for the proposed intervention and potential cost savings that may result from replacement of other intervention(s) currently covered by the health plan. Limited to the cost of intervention (acquisition, implementation and maintenance) <u>Possible sub-criteria:</u> Net cost of intervention; acquisition cost; implementation/ maintenance cost <i>Use scarce resources wisely to maximize health from a specific budget perspective</i></p>	<p><i>Reflects your institution's values (% yes): 88%</i> <i>Formally considered in appraisal process (% yes): 63%</i> <i>Sub-criteria specified:</i> net cost, potential additional costs, cost-effectiveness, cost-utility, budget impact on health plan <i>General comments:</i></p> <ul style="list-style-type: none"> • This criterion reflects the mandate of efficient and fair allocation of scarce healthcare resources • "Not a separate criterion, but part of the criterion "budget impact/opportunity cost" and the criterion "incremental cost-effectiveness" • Although many respondents view it as an important criterion, they comment that it is not a "legally binding" one. <p><i>Rare disease specificities:</i></p> <ul style="list-style-type: none"> • Often high cost per patient but relatively small budget impact • Issue of transparency in the price and costs of these interventions
<p>Comparative cost consequences – other medical costs Impact of the proposed intervention on other medical costs (excluding intervention cost) such as hospitalization, specialist consultations, adverse events costs, long-term care</p>	<p><i>Reflects your institution's values (% yes): 88%</i> <i>Formally considered in appraisal process (% yes): 75%</i> <i>General comments:</i></p> <ul style="list-style-type: none"> • This criterion reflects efficient allocation of healthcare resources • This criterion is considered as part of the appraisal process as a sub criterion for assessing the economic impact (ex. cost-effectiveness analysis, budget impact, opportunity cost analysis) .

Table 2. Continued

Criteria Definition, possible sub-criteria <i>Ethical foundation</i>	Participants' input
<p><u>Possible sub-criteria:</u> Impact on primary care expenditures; on hospital care expenditures; on long-term care expenditures</p> <p><i>Use scarce medical resources wisely from a broad perspective</i></p>	<ul style="list-style-type: none"> • This criterion can also be considered in terms of use of resources <p><i>Rare disease specificities:</i></p> <ul style="list-style-type: none"> • Broad range of medical resources and services used for patients with rare diseases
<p>Comparative cost consequences – non-medical costs Impact of the proposed intervention on non-medical costs such as disability costs, social services, lost productivity, caregiver time, etc.</p> <p><u>Possible sub-criteria:</u> Impact on productivity; financial impact on patients; on caregivers; costs to the wider social care system</p>	<p><i>Reflects your institution's values (% yes): 38%</i></p> <p><i>Formally considered in appraisal process (% yes): 38%</i></p> <p><i>General comments:</i></p> <ul style="list-style-type: none"> • This criterion seems to be considered as part of the appraisal process when the perspective of the healthcare system or the societal perspective is needed. • “Not systematically” considered in appraisal processes • One respondent raised the difficulty of assessing this criterion in a context of “budgetary silos”
<p><i>Preserve societal and individual resources wisely from a broad perspective</i></p>	<p><i>Rare disease specificities:</i></p> <ul style="list-style-type: none"> • Impact on social services, patient and caregivers' productivity and costs
<p>Opportunity costs and affordability Consideration of the medical resources that may be forgone (opportunity costs) if the intervention is implemented and whether the healthcare system can afford implementing the intervention. Both affordability and opportunity cost considerations require a financial/budgeting exercise. Opportunity costs and affordability can be considered at system/institution level and at the patient level.</p>	<p><i>Reflects your institution's values (% yes): 75%</i></p> <p><i>Formally considered in appraisal process (% yes): 50%</i></p> <p><i>General comments:</i></p> <ul style="list-style-type: none"> • This criterion reflects the efficient use of limited healthcare resources, the fairness of priority setting and justifies “implicit rationing”. • “This criterion is the most wanted for operationalization, but also the least operational for now”. • Respondents commented that this criterion reflected through budget impact and opportunity costs helps clarify “financing and implementation issues”. However, affordability is considered as the decision-maker's prerogative. • Many noted that this criterion is part of the assessment but not necessarily of the appraisal.
<p><u>Possible sub-criteria:</u> Opportunity costs (forgone resources) for patient; for population; affordability</p>	<p><i>Rare disease specificities:</i></p> <ul style="list-style-type: none"> • Consider opportunity cost of benefits forgone in other disease areas
<p><i>Principle of efficiency</i></p>	<ul style="list-style-type: none"> • Opportunity costs may be foregone disproportionately for rare compared to common diseases because the costs of commercial development of some products may be unavoidably high
<p>Mandate and scope of healthcare system Alignment of the intervention with the mandate/scope of the healthcare system. The goal of healthcare is to maintain normal functioning. Mission and scope of healthcare plans/systems derive from this principle.</p>	<p><i>Reflects your institution's values (% yes): 75%</i></p> <p><i>Formally considered in appraisal process (% yes): 25%</i></p> <p><i>General comments:</i></p> <ul style="list-style-type: none"> • Many commented that this criterion is made explicit in the mission, values or ethical foundations through a law, a regulation or published processes • Some participants noted that if an intervention is not within the scope of the healthcare system, it would not be selected for appraisal
<p><u>Possible sub-criteria:</u> NA</p>	
<p><i>Eth.Promote and protect the health of the population served</i></p>	<p><i>Rare disease specificities:</i></p> <ul style="list-style-type: none"> • Providing treatments for severe health conditions such as rare diseases is generally aligned with mandates
<p>Environmental impact The extent to which the production, use or implementation of the intervention causes environmental damage</p>	<p><i>Reflects your institution's values (% yes): 13%</i></p> <p><i>Formally considered in appraisal process (% yes): 13%</i></p> <p><i>General comments:</i></p>
<p><u>Possible sub-criteria:</u> Environmental impact of production; of use; of implementation</p>	<ul style="list-style-type: none"> • Many respondents considered that this criterion was outside of the remits of the organization or the scope of the assessment.
<p><i>Protect the environment</i></p>	<ul style="list-style-type: none"> • One respondent mentioned that it is an “explicit deliberative criterion”.
	<p><i>Rare disease specificities:</i></p> <ul style="list-style-type: none"> • Low impact

Table 2. Continued

Criteria Definition, possible sub-criteria <i>Ethical foundation</i>	Participants' input
Criteria representing the imperative of practical wisdom to make decision informed by relevant evidence and the specific context	
Quality of evidence	
Extent to which evidence on the proposed intervention is relevant to the decision-making body and valid with respect to scientific standards and conclusions (agreement of results between studies). This includes consideration of uncertainty. Consistent and complete reporting of evidence is a pre-requisite to assess validity.	<i>Reflects your institution's values (% yes): 100%</i> <i>Formally considered in appraisal process (% yes): 88%</i>
<u>Possible sub-criteria:</u> Validity; relevance; completeness of reporting; type of evidence	<i>Sub-criteria specified:</i> risk of bias, inconsistency, indirectness, imprecision, publication bias, validity; relevance; completeness of reporting
<i>Consider strength of claims about the intervention based on formal evidence</i>	<i>General comments:</i> • This criterion reflects scientific excellence and quality • Quality of evidence is described as “central” to the formulation of evidence-based recommendations <i>Rare disease specificities:</i> • Limited knowledge, high uncertainty • Clinical research is generally less common in children than in adults, although children are most often affected • Scarcity of data on rare diseases and orphan drugs
Expert consensus/clinical practice guidelines	
Concurrence of the proposed intervention with the current consensus of experts on what constitutes state-of-the-art practices in the management of the targeted health condition; guidelines are usually developed by means of an explicit process and are intended to improve clinical practice.	<i>Reflects your institution's values (% yes): 75%</i> <i>Formally considered in appraisal process (% yes): 75%</i>
<u>Possible sub-criteria:</u> NA	<i>General comments:</i> • This criterion reflects stakeholder involvement but also the relevance of the recommendations and its alignment with the ongoing practices thereby fostering legitimacy and acceptability • Experts contribute to evidence generation and the elaboration of recommendations <i>Rare disease specificities:</i> • Limited availability of clinical experts and guidelines
<i>Consider strength of claims about the intervention based on expert knowledge and consensus</i>	
System capacity and appropriate use of intervention	
The capacity of a healthcare system to implement the intervention and to ensure its appropriate use depends on its infrastructure, organization, skills, legislation, barriers and risks of inappropriate use. Such considerations include mapping current systems and estimating whether the use of the intervention under scrutiny requires additional capacities.	<i>Reflects your institution's values (% yes): 75%</i> <i>Formally considered in appraisal process (% yes): 63%</i>
<u>Possible sub-criteria:</u> Organizational requirements (e.g., process, premises, equipment); skill requirements; legislative requirements; surveillance requirements; risk of inappropriate use; institutional limitations to uptake; ability to reach the whole target region/population	<i>Sub-criteria specified:</i> Organizational requirements (e.g., process, premises, equipment); Skill requirements; Legislative requirements; Surveillance requirements; Risk of inappropriate use; Institutional limitations to uptake; Ability to reach the whole target region/population <i>General comments:</i> • This criterion reflects accessibility to healthcare, quality and safety of healthcare. It is “part of the state of medical practice” and conveys contextual information. • “Most important among contextual criteria” • “The full range of sub-criteria is considered when relevant” <i>Rare disease specificities:</i> • Lack of local expertise; difficulty in reaching whole target population; monitoring and surveillance requirements
<i>Ensure appropriate use of intervention to realize its potential benefit and avoid unintended consequences</i>	
Common goal and specific interests	
Pressures or barriers from groups of stakeholders or individuals are often part of the context surrounding healthcare interventions. Being aware of pressures and interests at stake and how they may affect decision making helps ensure that decisions are fair-minded.	<i>Reflects your institution's values (% yes): 50%</i> <i>Formally considered in appraisal process (% yes): 25%</i>
<u>Possible sub-criteria:</u> Stakeholder pressures; stakeholders barriers; conflict of interest	<i>General comments:</i> • This criterion is reflected through procedural fairness (i.e. stakeholder involvement, transparency of processes) • One participant noted that this criteria might not be “easily assessable” <i>Rare disease specificities:</i> • Highly engaged patient organizations

Table 2. Continued

Criteria Definition, possible sub-criteria <i>Ethical foundation</i>	Participants' input
<i>Awareness of stakeholder pressures / barriers helps ensure that decisions are fair-minded and driven by the common goal and not unduly influenced by special interests</i>	
<p>Political/historical/ cultural context The political, historical or cultural context may influence the value of an intervention with respect to specific political situations and overall priorities (e.g., priority for innovation) as well as habits, traditions and precedence.</p> <p>Possible sub-criteria: Political priorities and context; cultural acceptability; precedence (congruence with previous and future decisions); impact on innovation & research; impact on partnership & collaboration among healthcare stakeholders</p>	<p><i>Reflects your institution's values (% yes): 50%</i> <i>Formally considered in appraisal process (% yes): 50%</i></p> <p><i>General comments:</i></p> <ul style="list-style-type: none"> • This criterion is considered implicitly as part of the deliberative process or for example for public health interventions like HPV vaccination or in relation with financial priorities. • One respondent noted that the sub-criterion of precedence is explicitly considered to ensure consistency across decisions • One participant remarked on the difficulty of operationalizing this criterion • One respondent specified that "innovation & research" are taken into account although not through a formal process (18).
<i>Awareness of political/ historical/cultural aspects to ensure that decisions are based on a broad understanding of the context</i>	<p><i>Rare disease specificities:</i></p> <ul style="list-style-type: none"> • Impact on innovation; precedence • Consider local laws or specific mandates for rare diseases if applicable in specific contexts

Keeping these two concepts distinct in a value measurement framework allows prioritization of interventions for severe diseases and with unmet needs. All respondents reported that *Unmet needs* reflected their institutions' values, which was linked to the goal of improving quality of care, and 75 percent stated it was formally considered. Lack of treatment alternatives for a very severe disease (often the case for rare diseases) was noted as a strong argument in favor of coverage, and one participant reported that this criterion was explicitly formalized for patients with rare diseases. These criteria were not mentioned by participants in the exploration of mottos and mandates, possibly because they reflect an implicit motivating value of healthcare, rooted in compassion (15).

Size of affected population, rooted in the imperative of *doing the greatest good for the greatest number*, was deemed by 63 percent of participants to reflect the values of their institutions. However, more institutions (88 percent) formally considered this criterion, as it was deemed relevant with respect to efficient use of healthcare resources (e.g., size of budget impact). Furthermore, consideration of the size of the population prompted reflections on the role of rarity in resource allocation. It was first noted that rarity is not an indicator of low value of an intervention but also not necessarily of high value, as arguments based on "rights to access" to beneficial therapies are deemed stronger than those based on small population size.

Participants also pointed out that all rare diseases combined represent a significant population. Comments highlighted the

debate on trade-offs between the imperatives to alleviate patient suffering, serve the whole population equitably and uphold sustainability, and the challenges to resolve this tension, in particular for rare diseases. This criterion was not mentioned *per se* in the narrative exploration (Table 1) but triggered a reflection on the social values at stake.

In quest for equity and applying the principle of first helping those who are worst off, societies may prioritize populations that are particularly disadvantaged and face specific challenges in their communities. This type of prioritization, captured by the criterion *Population priorities and access*, largely depends on local context and values, as opposed to universal prioritization based on disease severity and unmet medical needs. Most participants (88 percent) reported that this criterion reflected their institutions' values. Indeed one stated that "Consideration of ethical issues, including equitable distribution among vulnerable groups is a core deliberative criterion." However, only 38 percent reported that this is formally considered. Participants noted that regulatory, and other, policies reflect prioritization of rare diseases (e.g., orphan designation) and that some agencies give special consideration or have developed special approaches to rare diseases. However, approaches to value assessment for rare diseases that profoundly deviate from established general principles were questioned.

Criteria Representing the Imperative to Uphold Healthcare System Sustainability. The majority of participants (88 percent) reported that the criteria *Comparative cost consequences – Cost of intervention*

as well as *Other medical costs* reflected their institutions' values. These criteria aim at upholding sustainability and, according to participants, are expressed in the mandate to efficiently allocate scarce healthcare resources. A majority of respondents (63 percent and 75 percent, respectively) indicated that both criteria are formally considered, but, as comments revealed, often only in combined measures such as budget impact or cost-effectiveness.

Comments also highlighted that the best way to consider the different economic aspects involved in the evaluation of an intervention remains a subject of debate fueled by several current controversies (3). Regarding rare diseases, participants noted that, although treatments are often associated with a high cost, small population size limits their budget impact. They also pointed out that "patients with rare diseases require a broad range of medical resources and services," which highlights the importance of considering the cost of the intervention that is evaluated and other associated medical costs separately.

Fewer than half of participants (38 percent) reported that the criterion *Comparative cost consequences – nonmedical costs* reflects their institutions' values or is formally considered. The ethical underpinning of this criterion is the call to preserve societal and individual resources from a broad perspective. Thus it raises the important question of the perspective from which the appraisal is to be conducted. Respondents commented that, although sometimes a societal perspective is needed, there are difficulties in taking this wider perspective "in the context of budgetary silos."

The criterion *Opportunity costs and affordability* requires exploring the budget impact of the intervention and potential foregone resources following its implementation with the aim of ensuring healthcare system sustainability. A majority of participants (75 percent) recognized that this criterion was reflected in their institutions' values, commenting that it is targeted toward efficient use of limited healthcare resources and justifies "implicit rationing." Half of participants said that "opportunity costs and affordability" was formally considered in their appraisal process, but it was also noted that, although of key importance, it is currently "the most difficult criterion to operationalize." Others noted that opportunity costs are assessed through budget impact analysis to help clarify financing issues. One participant indicated that "affordability was not deemed to be part of the appraisal but pertained to the decision-making process." It was noted that "opportunity costs may be foregone disproportionately for rare compared with common diseases because the costs of commercial development of some products may be unavoidably high."

Mandate and scope of the healthcare system refers to the overall foundation of healthcare and is also a fundamental aspect of healthcare system sustainability. This criterion was viewed by participants as expressed in their respective institution's mission, values, or ethical foundations and stipulated through law or regulation; 25 percent of participants indicated

that this is formally considered. This criterion was perceived more as a selection tool for interventions to be appraised rather than part of the appraisal process *per se*. However, it was acknowledged that some interventions (e.g., *in vitro* fertilization, growth hormone treatment) may be challenging with regard to a specific healthcare system's mandate and scope and, therefore, would require an explicit consideration of this criterion.

Sustainability in its widest sense includes environmental considerations. Few participants (13 percent) regarded the criterion *Environmental impact* as reflected in their institutions' values or as considered in the appraisal, because it was generally deemed to be outside the remit of their organizations.

Criteria Representing the Imperative to Make Decisions Informed by Relevant Evidence and the Specific Context. *Quality of evidence* considers, based on evidence, the strength of claims about an intervention and includes the important element of relevance to the context of the decision. All respondents confirmed that this criterion reflected their institutions' values, and 88 percent reported that it was formally considered. According to participants, this criterion reflected scientific excellence and was central to the ability of their institutions to formulate evidence-based recommendations, thus linking the credibility and, hence, legitimacy of their recommendations to the quality of evidence. The lack of knowledge about rare diseases and resulting uncertainty regarding the potential benefits and risks of treatments create a challenge for decision makers.

Expressing another aspect of considering the strength of claims about an intervention in a given context, which is based on expert knowledge and consensus, the criterion *Expert consensus/CPGs* was reported by 75 percent of participants to reflect their institutions' values and to be formally considered. Participants noted that this criterion calls for involvement of experts and integration of expert knowledge beyond formal evidence to help ensure that decisions are relevant to the contextual clinical practice, thereby supporting their legitimacy and acceptability.

System capacity and appropriate use in a given context was deemed by the majority of respondents (75 percent) to reflect their institutions' values and also to be formally considered in their appraisal process. Participants stressed the importance of this criterion and most of its sub-criteria, and drew a link to multiple concepts, including accessibility, quality, and safety of healthcare delivery and "contextual information," which highlights the variety of system-related considerations that play a role in appraisals.

Awareness of stakeholder pressures and barriers in a given context (criterion *Common goal and specific interests*) helps ensure that decisions are fair-minded and driven by the common goal rather than special interests. Reflecting on this criterion, half of participants noted that this is aligned with their institutions' values, but only 25 percent noted that it is explicitly considered in the appraisal process. Participants com-

mented that this criterion is reflected in the pursuit of procedural fairness, which, among others, includes operationalizing the principles of stakeholder involvement and transparency.

Awareness of the “political/historical/cultural context” was deemed by half the participants to be reflected in their institutions’ values and formally considered. However, participants noted that, apart from public health interventions, this criterion is often only implicitly considered. Participants also commented that the sub-criteria “*Precedence*” (i.e., previous decisions on similar interventions) and “*Innovation and research*” are both considered, the latter though not through a formal process.

When prompted to suggest additional criteria, participants mentioned the transparency of the reasoning and transparency of evidence used in decision making. Of note, both of these considerations are implicit in multicriteria approaches (13;16;17).

Quantitative Values Elicitation Exercise and Exploration of Trade-Offs

The quantitative values elicitation exercise (Figure 2) revealed that, without explicitly established priorities (column A), at the group level, criteria representing the imperative “to alleviate or prevent patient suffering” (i.e., Effectiveness, Safety, PRO, Type of benefit) had the largest cumulative weight (35 percent), followed by criteria representing the imperatives “to serve the whole population equitably” (i.e., Disease severity, Unmet needs, and Size of population) (24 percent), “to uphold healthcare system sustainability” (i.e., Cost of intervention, Other medical costs, Nonmedical costs) (22 percent), and “to make decisions informed by evidence and context” (i.e., Quality of evidence, Expert consensus) (19 percent).

Some participants commented that such an approach, while it highlighted the difficulty of balancing the imperatives, may help clarify individual reflection and support the ethical reasoning regarding trade-offs, and the graphical representation might be helpful to share it with others.

Country-specific population priorities are established by healthcare authorities to operationalize the principle of equity (or fairness) within the context of a country’s value system. The appropriateness of including an explicit quantitative criterion to reflect trade-offs if priorities are established (including priorities for rare diseases) was discussed. It was noted that “this might lead to a fragmentation of the population and, therefore, it might be more appropriate to keep specific population priorities as a qualitative consideration.” It was also acknowledged that the way population priorities are considered in the decision process needs to be reflected upon.

To explore how the balancing act of decision making might be modified when priorities are established, and to provide a visual illustration of trade-offs, participants repeated the values elicitation exercise with the same criteria set but to which

a country-specific “Priorities” domain had been added, which expresses an additional aspect of the imperative to serve the population equitably (column B in Figure 2). Participants who assigned some weight to this domain (half assigned a weight of 0), traded primarily from a reduction in the relative importance of criteria representing the imperative “to make a decision informed by evidence and context” (Quality of evidence, Expert consensus) and of criteria representing the imperative to “alleviate or prevent patient suffering” (Effectiveness, Safety, Type of benefit). At the criteria level, the greatest trade-offs came from *Unmet needs* and “Quality of evidence.”

DISCUSSION

Reflective multicriteria is useful to explore substantive values of HTAs, to reflect on how these values and their ethical underpinning can be operationalized into decision criteria and to explore the trade-offs particularly critical for rare diseases, and at the heart of the healthcare debate.

The narrative approach revealed a diversity of substantive and procedural values with a common emphasis on scientific excellence, stakeholder involvement, independence, and transparency, with the greater purpose of providing quality care, serving the population, and optimal use of healthcare technology for best resource allocation. Complementary to the narrative approach, the reflective multicriteria approach allowed some elucidation of the substantive values of decision making, that is, the criteria that are considered along with their ethical underpinnings. It also revealed implicit criteria, such as *Unmet needs* and *Disease severity*, which are rooted in compassion (15) and were not mentioned in the narrative approach. Of note, multicriteria frameworks may be operationalized to also integrate several procedural values, including participative process for deliberation, clarity and transparency, consistency, and clear communication of reasoning and decision rationales (13;16;17), which was not explored in this study and calls for further research.

Examining the ethical aspects underpinning the criteria was deemed useful by participants to explore their institutional values. Except for *Environmental impact* and *Nonmedical costs*, most criteria were deemed to reflect the values of HTA agencies. By further revealing the founding values of HTA organizations, the analysis allowed exploration and identification of potential discrepancies between the substantive values articulated in their organizations’ mission and the processes in place to operationalize these values; indeed although most criteria were deemed to reflect institutions’ values, 70 percent of the criteria were reported by at least half of participants to be considered formally by their institutions.

Discussion revealed the need to incorporate criteria that pertain to the decision-maker remit (contextual criteria of EVIDEM) into the HTA process to support ultimate decision makers (e.g., Ministry of Health) in optimizing legitimacy of

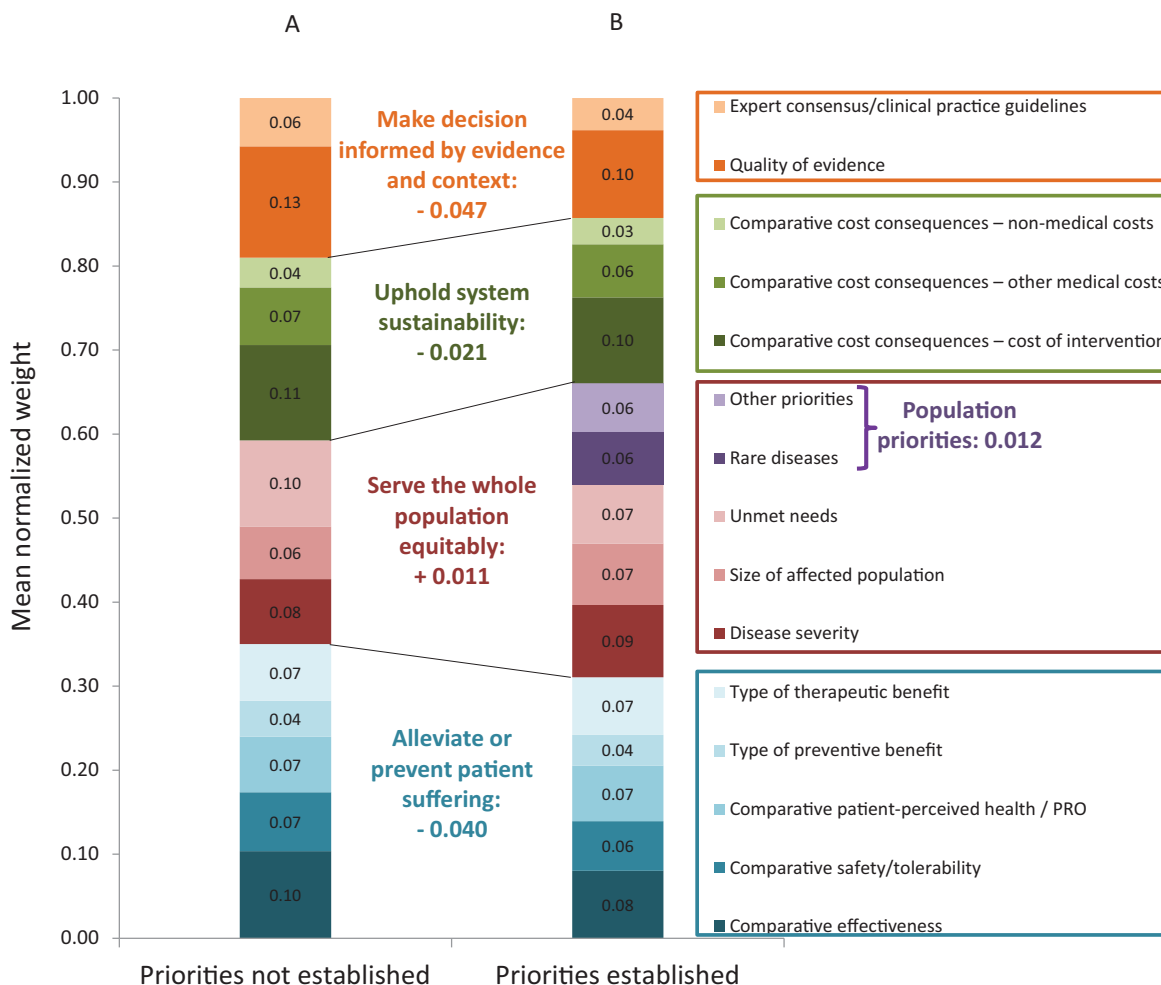


Figure 2. Exploration and visualization of trade-offs between a context when no country-specific priorities are established (A) and a context when country-specific priorities are established (B) (comparison of mean normalized weights elicited through hierarchical point allocation).

decisions. This is in line with the recent recommendation of Daniels for an “expanded HTA” to support accountable decision making (9). Opportunity cost was noted as a key aspect, albeit most difficult to operationalize, that needs to be integrated in the decision process to tackle ethical dilemmas.

The need to clarify how economic aspects are considered was also noted in line with the long-term quest to address the controversy around cost considerations (1); indeed the cost-effectiveness ratio does not support a distinct consideration of the different concepts regarding the types of costs (e.g., cost of intervention, other medical costs, nonmedical costs) (3). The challenges associated with considering the patient perspective was also raised. This is emphasized by the lack of relevant data but must be advanced to truly integrate the patient perspective.

Furthermore, the notion of precedence was noted as an important aspect of the decision process, usually considered informally, but which may have a key impact on decisions. These considerations are fully relevant to assessing treatments for rare diseases, where the basic tension between the aims of alleviating patient suffering, serving the whole population equitably,

and upholding healthcare sustainability (1) is particularly intense and can lead to ethical dilemmas. Thus, awareness of the underpinning ethical imperatives plays a key role when making trade-offs.

The quantitative values elicitation exercise highlighted the difficulty of balancing the imperatives to *alleviate or prevent patient suffering*, *serve the whole population equitably*, *uphold healthcare system sustainability*, and *make decisions informed by evidence and context*. The study suggest that such exercise can support individual reflection and clarify trade-offs by prompting the decision maker to express his/her thinking numerically and visualize it (along with the narratives). The visual representation can then be shared with others to facilitate the conversation to understand each other’s reasoning and values. Approached this way, rather than transforming reflection into an algorithm, quantitative values elicitation serves as visualization of the ethical argumentation behind a decision and can assist in clarifying the decision rationale (a hallmark of a fair process) (6), and better communicating it. Not replacing the inherently narrative aspect of ethical argumentation, trade-off visualization needs to remain a support to this conversation.

Exploring trade-offs in general and with respect to priorities, such as rare diseases, was challenging, which highlights the need to further reflect on the best way to account for trade-offs and consider population priorities that can be shared and agreed upon with the society at large. Moving beyond the current implicit (“gut feeling”) approach to trade-offs, incorporation of *Population priorities* as a quantitative criterion is a possible way forward to make the reasoning behind the redistribution of weights across criteria and their ethical imperatives explicit, but such an approach requires further research and consultation.

Awareness of the trade-offs between the key ethical imperative, facilitated by comprehensive and reflective multicriteria, is a step toward tackling ethical dilemmas to foster legitimacy and support health system governance. The generic nature of EVIDEM can provide a structure to capture the diversity of individual values and perspectives (interpretive frames) (6) for each coverage decision, thus facilitating, in a pragmatic manner, collective deliberation on how ethical dilemmas might be resolved. Such shared reasoning is necessary to reach a decision that all stakeholders would deem fair and reasonable, because it would be based on a wide reflective equilibrium (6).

Combining a fair deliberative process with reflective multicriteria is well suited to operationalize agencies’ procedural and substantive values to foster accountable and reasonable decisions, a prerequisite for their acceptability and successful implementation. It is argued that the ethical framework A4R combined with multicriteria approaches rooted in the fundamental objectives of healthcare systems could provide a pragmatic way for HTA agencies to support policy makers in their quest for legitimacy (19), and serve as a reminder that compassion is the ultimate legitimacy of all healthcare endeavors.

This exploratory study suggests that further research is warranted on how values on which HTA agencies are founded can be identified and operationalized in processes that support dealing with the basic tension at the heart of the healthcare debate, alleviating patient suffering, serving the whole population equitably, and upholding healthcare sustainability, while applying practical wisdom to make a legitimate decision adapted to the context.

CONFLICTS OF INTEREST

Authors Goetghebeur, Wagner, Samaha, O’Neil, and Badgley report received a research grant from Genzyme. Authors Abrishami, Sarria-Santamera, and Cleemput have nothing to disclose. Authors Castro-Jaramillo and Tringali received a travel grant from the EVIDEM Collaboration

REFERENCES

1. Sabin JE, Cochran D. Confronting trade-offs in health care: Harvard Pilgrim Health Care’s organizational ethics program. *Health Aff (Millwood)*. 2007;26:1129-1134.
2. Berwick DM, Nolan TW, Whittington J. The triple aim: Care, health, and cost. *Health Aff (Millwood)*. 2008;27:759-769.
3. Neumann PJ, Cohen JT. Measuring the value of prescription drugs. *N Engl J Med*. 2015;373:2595-2597.
4. Wagner M, Khoury H, Willet J, Rindress D, Goetghebeur M. Can the EVIDEM framework tackle issues raised by evaluating treatments for rare diseases: Analysis of issues and policies, and context-specific adaptation. *Pharmacoeconomics*. 2016;34:285-301.
5. Tambuyzer E. Rare diseases, orphan drugs and their regulation: Questions and misconceptions. *Nat Rev Drug Discov*. 2010;9:921-929.
6. Daniels N, van der Wilt GJ. Health technology assessment, deliberative process, and ethically contested issues. *Int J Technol Assess Health Care*. 2016;32:10-15.
7. Biron L, Rumbold B, Faden R. Social value judgments in health-care: A philosophical critique. *J Health Organ Manag*. 2012;26:317-330.
8. Clark S, Weale A. Social values in health priority setting: A conceptual framework. *J Health Organ Manag*. 2012;26:293-316.
9. Daniels N, Porteny T, Urritia J. Expanded HTA: Enhancing fairness and legitimacy. *Int J Health Policy Manag*. 2015;5:1-3.
10. Daniels N, Sabin J. Limits to health care: Fair procedures, democratic deliberation, and the legitimacy problem for insurers. *Philos Public Aff*. 1997;26:303-350.
11. Baltussen R, Jansen MP, Mikkelsen E, et al. Priority setting for universal health coverage: We need evidence-informed deliberative processes, not just more evidence on cost-effectiveness. *Int J Health Policy Manag*. 2016;5:615-618.
12. Hofmann B, Cleemput I, Bond K, Kronen T, Droste S, Sacchini D et al. Revealing and acknowledging value judgments in health technology assessment. *Int J Technol Assess Health Care*. 2014;30:579-586.
13. Goetghebeur MM, Wagner M, Khoury H, et al. Evidence and value: Impact on DEcisionMaking—the EVIDEM framework and potential applications. *BMC Health Serv Res*. 2008;8:270.
14. Tanios N, Wagner M, Tony M, et al. Which criteria are considered in healthcare decisions? Insights from an international survey of policy and clinical decision makers. *Int J Technol Assess Health Care*. 2013;29:456-465.
15. Fotaki M. Why and how is compassion necessary to provide good quality healthcare? *Int J Health Policy Manag*. 2015;4:199-201.
16. Baltussen R, Niessen L. Priority setting of health interventions: The need for multi-criteria decision analysis. *Cost Eff Resour Alloc*. 2006;4:14.
17. Thokala P, Devlin N, Marsh K, et al. Multiple criteria decision analysis for health care decision making - An introduction. Report 1 of the ISPOR MCDA Emerging Good Practices Task Force. *Value Health*. 2016;19:1-13.
18. Baeroc K, Baltussen R. Legitimate healthcare limit setting in a real-world setting: Integrating accountability for reasonableness and multi-criteria decision analysis. *Publ Health Ethics*. 2014;7:98-111.
19. Goetghebeur MM, Castro Jaramillo H, Baltussen R, Daniels N. The art of priority setting. *Lancet*. 2017;389:2368-2369.