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ARTICLE

How should medicines reimbursement work? The views of Spanish experts

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Abstract

Although the criteria that support reimbursement decisions for medicines are often set by legislation, as is the case in Spain, in many cases neither the definition nor the measurement methods for these criteria are provided. Our goal was to elicit the views of a large sample of Spanish technical specialists on how to evaluate each one of the criteria that inform pricing and reimbursement decisions in Spain. Professionals from various stakeholder groups involved in health economics, health technology assessment, and industry participated in a survey. Participants recommended that reimbursement decisions should take specific account of unmet medical need and rare diseases. Health benefit should be measured using quality-adjusted life-years. There should be an explicit cost-effectiveness threshold, and this threshold should take account of population groups and special situations.

Keywords: health technology assessment; pharmaceutical policy; pricing and reimbursement

1. Introduction

Countries around the world face similar questions when it comes to shaping their health technology assessment (HTA) and their pricing and reimbursement (P&R) systems. Amongst other concerns, they need to consider the criteria to apply in P&R decisions, and the evidence and methodologies used in HTA to measure those criteria. Some countries, such as England and Wales, provide detailed methodological guides for developers and document the reasons for their decisions (NICE, 2024), but others are less transparent (Oliva-Moreno *et al.*, 2020; Comité Asesor para la Financiación de la Prestación Farmacéutica del SNS (CAPF), 2022).

In Spain reimbursement decisions for new medicines in the Spanish National Health System (NHS) should be made considering six criteria (Ley 29/2006, de 26 de julio, 2006; Real Decreto Legislativo, 1/2015 de 24 de julio, 2015; Vogler, 2020):

(a) Severity, duration, and sequelae of the different pathologies for which they are indicated;
(b) Specific needs of certain groups;
(c) Therapeutic and social value of the medicine and its incremental clinical benefit, taking into account its cost-effectiveness;
(d) Rationalisation of public spending on pharmaceuticals and budgetary impact on the NHS;

(e) Availability of medicines or other therapeutic alternatives for the same conditions at a lower price or lower treatment cost;
(f) Degree of innovation of the new medicine.

Although the law originally came into effect in 2006 (Ley 29/2006, de 26 de julio, 2006) (and was redrafted various times in the following decade), there is still a lack of regulatory development to define and measure the criteria outlined above. This has led to concerns of methodological incoherence in the evidence, and that decisions lack transparency, predictability, and consistency (Oliva-Moreno *et al.*, 2020; Vida *et al.*, 2023). In other words, in Spain the first question listed above (what criteria should support P&R decisions) has been answered, but the second (how should we measure them) has not.

Principles of good practice for HTA recommend assessment criteria and instruments that facilitate a broad focus and promote fair and transparent P&R decisions (Drummond *et al.*, 2008, 2012; Costa-Font *et al.*, 2017). Additionally, countries in the European Union (EU) will need to adapt to the new European regulation on HTA (Proposal for a Directive of the European Parliament and of the Council, 2023). Hence, the present moment is favourable for exploring the options that could be used to define and measure the criteria for decision-making in Spain. This could not only inform the reforms currently being implemented for HTA in Spain (Ministerio de Sanidad, 2024b), but it could also serve as inspiration for other countries embarking on a similar journey towards implementing greater levels of transparency, consistency, and robustness in their systems. As a contribution to this debate, this paper presents the results of a survey distributed to technical specialists working in health technology evaluation in the Spanish regulatory body, national and regional HTA agencies, hospital pharmacy, ministry of health and industry. Hence the survey does not claim to represent the views of all stakeholders. The aim was to capture the perspectives of a relatively homogenous group of technical specialists with hands-on expertise and familiar with the issues and the debates. A survey aimed at other groups would not be able to frame such detailed questions on scientific-technical aspects of the law. Moreover, we might expect people with this profile to aspire to attributes of competence (technical knowledge, understanding of the policy making process, and ability to communicate complex ideas); integrity (independence and faithful reporting of research) (Vermeule, 2008); and benevolence (commitment to the principles of public service) (Haynes *et al.*, 2012). The technical perspective offers valuable insights for democratic policy making. Citizens tend to positively view the participation of technical specialists in policy design and implementation (Bertsou, 2022).

The survey enquired about the optimal ways of measuring the criteria specified in Spanish law that ought to support reimbursement decisions. We also sought input on the weighting of these criteria in reimbursement decisions, their appropriateness for informing such decisions, and the potential inclusion of additional criteria (especially the patient experience) to the existing list.

With this paper, we report empirical evidence of the views of technical experts with knowledge of the Spanish P&R system on the range of issues described above. Similar studies, focusing on Spain (Calleja and Badia, 2022; Zozaya *et al.*, 2022) and elsewhere (Le Pen *et al.*, 2003; Franken *et al.*, 2015; Iskrov and Stefanov, 2016; Schmitz *et al.*, 2016; Detiček *et al.*, 2018; Rejon-Parrilla *et al.*, 2022), have solicited views of a broad range of stakeholders on what the criteria should be, or focused on the P&R process, or examined case studies of specific health technologies (Le Pen *et al.*, 2003; Schmitz *et al.*, 2016; Detiček *et al.*, 2018) To our knowledge, no previous research has elicited the views of experts on how to measure the reimbursement criteria.

2. Methodologies for measurement of criteria for reimbursement

This section reviews the methodological options recommended in the literature or used by other countries for measuring criteria similar to those listed in the Spanish law.

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2.1 Severity

Several countries, such as Belgium, France, the Netherlands, and Sweden (Franken *et al.*, 2015), consider the severity of the disease as a factor in deciding price or reimbursement. One way of defining severity is the use of the absolute quality-adjusted life-year (QALY) shortfall (the number of QALYs an individual can expect to lose in years to come as a result of living with a given condition) (Arneberg, 2012) and the proportional QALY shortfall (proportion of future QALYs someone can expect to lose as a result of living with a given condition, taking their total remaining life expectancy as the total possible maximum if lived in full quality of life) (Stolk *et al.*, 2004). For instance, in England, National Institute for Health and Care Excellence (NICE) recently introduced a new severity-modifier that allows committees to weight QALYs more when gained in patients with more severe diseases (McNamara *et al.*, 2023). In Norway, severity is formally captured through the absolute shortfall approach (Ottersen *et al.*, 2016; Norwegian Medicines Agency, 2018), which estimates the number of future QALYs that someone living with a condition is expected to lose as a result of it, under current care conditions, and consequently for more severe conditions Norway accepts higher cost-effectiveness ratios (Norwegian Medicines Agency, 2018). In the Netherlands, they introduced the proportional shortfall as an equity approach combining aspects of fair innings (advocates that everyone is entitled to a 'fair' span of life or health, weighting QALY gains more in younger persons and less in relatively older ones) and prospective health (expected life expectancy regardless of how much one has lived so far) (Van de Wetering *et al.*, 2013). Despite these guidelines, a recent study exploring the priority setting criteria cited by Dutch appraisal committee reports showed that severity of illness was not referenced at all in Dutch HTA reports between 2013 and 2016 (Reckers-Droog *et al.*, 2018).

2.2 Special needs

Decision makers across Europe have given particular consideration to groups of patients such as those close to the end of their life, children, rare diseases, and unmet need. Each of these situations has been addressed by European Pharmaceutical Regulation (Proposal for a Directive of the European Parliament and of the Council, 2023) or HTA bodies in other countries (Hughes *et al.*, 2005; Vreman *et al.*, 2019; Denburg *et al.*, 2020; Bovenberg *et al.*, 2021; Mills and Kanavos, 2022). NICE introduced the end-of-life criteria in 2009, allowing treatments at the end of life to be funded with incremental cost-effectiveness ratios (ICERs) over the regular threshold (Bovenberg *et al.*, 2021), though replaced it with the severity modifier in 2022 (Charlton *et al.*, 2022). The European Medicines Agency (EMA) provides a definition of orphan medicines (EMA, 2023), which is not exactly the same as medicines indicated for ultra-rare diseases (Hughes *et al.*, 2005; Badia *et al.*, 2019). European payers tend to pay premium prices for orphan medicines (Michel and Toumi, 2012; Medic *et al.*, 2017). Several countries consider unmet need in their pricing policy (World Health Organization, 2015). The proposed new European pharmaceutical regulation adds another layer of potential rewards to manufacturers, since it provides extensions of periods of market exclusivity (which should translate into increased rates of return) for orphan and paediatric medicinal products and those responding to unmet needs (Proposal for a Directive of the European Parliament and of the Council, 2023).

The assessment of technologies aimed at treating children present distinct challenges (Denburg *et al.*, 2020; Moretti *et al.*, 2022). One such challenge is the difficulty in measuring quality of life in children, with one paper arguing that this difficulty could penalise paediatric populations in utilitarian systems that assume QALY gains to be equal across a population if the quality of the evidence is indeed poorer or scarcer than in adults (Ungar *et al.*, 2013). Petrou (2010), for instance, suggested that society may value health gains in children more than in adults.

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Unmet need, as per the definition provided in Article 83 of the new European pharmaceutical legislation (Proposal for a Directive of the European Parliament and of the council, 2023; Commission Regulation (EC), 2006), has been an area that has received considerable attention in European health policy. The EMA established the priority medicines scheme (PRIME) in March 2016 to expedite the development and approval of promising products aimed at treating diseases with high unmet medical need (Mullard, 2017). By June 2018, the EMA had awarded PRIME status to 39 therapies (Neez *et al.*, 2020). The new European pharmaceutical legislation contemplates rewarding manufacturers of medicinal products addressing unmet medical needs with the application of accelerated assessment mechanisms and the prolongation of data protection and subsequently of market exclusivity (Proposal for a Directive of the European Parliament and of the Council, 2023). In Spain this group has been defined as population living with a serious pathology for which there is a therapeutic gap (Comisión Permanente de Farmacia del Consejo Interterritorial del SNS, 2020).

2.3 Therapeutic and social value

There are different ways of measuring therapeutic value. One possible approach, taken in France for instance, would consist of translating clinical criteria into a common barometer for comparison across all pathologies. In France this is operationalised by quantifying clinical value (SMR) and clinical added value (ASMR). The SMR assesses a drug's clinical benefit on a 4-level scale from 'insufficient' to 'important', determining its reimbursement rate by national health insurance. The ASMR evaluates added clinical value on a 5-level scale from 'no therapeutic progress' to 'major therapeutic progress', influencing the price the manufacturer can negotiate with the Committee of Health Products (Haute Autorité de Santé, 2014; Kergall *et al.*, 2021). An alternative approach to measuring therapeutic value is the use of health-related quality of life measurement and valuation, approach taken for instance by NICE (Dawoud *et al.*, 2022) and the Dutch National Health Care Institute (Zorginstituut Nederland) (Vallejo-Torres *et al.*, 2022). The QALY measures therapeutic value by assessing gains in both life quality and lifespan, enabling cross comparisons of health interventions (Whitehead and Ali, 2010).

Sweden and some other countries use a societal perspective to capture non-health benefits in economic evaluations (Svensson *et al.*, 2015; Avşar *et al.*, 2023).

2.4 Budget impact

Budget impact analysis (BIA) is a measure of the impact that the introduction of a new technology has on the budget of a health care system. A 3–5 year time horizon is usually recommended (Trueman *et al.*, 2001; Servei Català de la Salut, 2014). Several Spanish HTA reports have only measured pharmaceutical costs. We asked whether BIA should take the perspective of the pharmaceutical sector or costs accruing to the health care sector as a whole.

2.5 Availability of therapeutic alternatives

Spanish pharmaceutical law requires that decision makers take into account in the P&R of a new medicine whether there is a therapeutic alternative at lower cost than the new medicine. The idea being that, in situations when a new medicine is requesting reimbursement at a given price and there is an equivalent alternative on the market, the health care system will never pay more for the new medicine (Schneeweiss, 2007). In Australia, programmes based on defining options with therapeutic equivalence have shown saving for their health care systems (Chynoweth and Larmour, 2019). This raises the question of what should be meant by a 'therapeutic alternative' in Spanish law.

There is considerable literature about how to prove therapeutic equivalence (Kirshner, 1991; Röhmel, 1998; Chow and Shao, 2002; Sánchez *et al.*, 2007; Chen *et al.*, 2011; Murray *et al.*,

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2016; Cappello *et al.*, 2020). Some work has centred on the concept of 'interchangeable' equivalents (Alegre del Rey *et al.*, 2014). There is some debate about whether a 'therapeutic equivalent' should include non-authorised uses of a therapy (off-label). There may be 'galenic' differences, referring to differences in the method of administration which may be appreciated by patients but which do not translate into measurable improvements in clinical outcomes.

The World Health Organisation (WHO) provides a taxonomy of Anatomical, Therapeutic, and Chemical Classification (ATC) which may provide another way of thinking about therapeutic alternatives. The ATC is a coding system for medicines according to their pharmacological effect, therapeutic indications, and chemical structure, divided into five levels: the first level (ATC1) is the most general and the fifth level (ATC5) the most detailed. Substances in the same group at level 4 share the same 'chemical subgroup' (e.g. statins) while pharmaceuticals at level 5 contain the same chemical substance (e.g. atorvastatin) (World Health Organization, 2009; Ministerio de Sanidad, 2020). The ATC system is, however, not strictly a therapeutic classification system. The ATC allows drugs with several therapeutic uses to be included in the same 1st, 2nd, 3rd, and 4th level groups without specifying the main indication.

2.6 Degree of innovation

The degree of innovation is listed as a reimbursement criteria in Spain but not defined. Several other countries state that they take account of the degree of innovation in their P&R decisions (e.g. Italy, England and France). However, in Italy, 'innovation' overlaps with the concept of added therapeutic value, which risks 'double counting' the benefit. The degree of innovation, considered independently from other criteria that already inform reimbursement decisions, is a complex concept to define, measure, and articulate in decision-making systems. Previous research approached this issue and came up with a conceptual construct that could inform such decisions in Spain, considering what other criteria are listed as relevant in our system (Rejon-Parrilla *et al.*, 2022), and developed a definition of degree of innovation that includes: step-change; convenience; strength of evidence base taking into account the degree of uncertainty associated with the evidence (amongst other factors); impact on future R&D (i.e. how the research that went into developing the technology at hand might enable future innovations). To our knowledge, NICE is the only HTA institution that defines the degree of innovation independently from other concepts that traditionally have informed reimbursement decisions, such as therapeutic value, cost-effectiveness, or whether they respond to an unmet medical need (Vogler, 2022). The definition of degree of innovation is made in the context of how it can inform their decision making, establishing three conditions to class a new medicine as innovative (Charlton and Rid, 2019; Rejon-Parrilla *et al.*, 2022): (i) the technology must display 'innovative characteristics' or be of an 'innovative nature'; (ii) the innovative nature of the technology must bring substantial health benefits to the patient, also referred to as a '"step-change" in the management of the condition'; and (iii) the substantial benefits brought by the innovative characteristics of the health technology must not already be captured in the ICER calculation of the technology under scrutiny and they must be 'demonstrable and distinctive'.

3. Data and methods

3.1 Data

The evidence is collected from a survey (see Annexes I and II) distributed to members of scientific, professional, academic, and industry organisations that participate in the HTA process at the national or regional level in Spain (more information about the distribution of the survey in Annex III). We do not know if the respondents themselves participate in HTA (this information is confidential) but are likely to be colleagues of people who do, or to have a professional interest and opinion about the HTA process. We believed that this group (rather than patients or citizens)

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would be familiar with the technical nature of the questions which were our object of interest (Rowe and Calnan, 2006).

The survey was designed by the authors of this paper. We drafted a first version, which we circulated to four experts to pilot it and refine it. These experts included two health economists, one hospital pharmacist, and a director of an industry association. We used the online software Tally (https://tally.so/) to construct the survey. We drafted an email that included an invitation letter and a link to the survey. In order to facilitate distribution, we made use of contacts in each interest group.

We circulated the survey on the 9 May 2022, giving initially 2 weeks to respond. We sent two reminders between the 9 May and the 23 May, and on request allowed one more week.

The survey was designed and distributed in Spanish. The survey consisted of four blocks of questions. First, an initial section asking respondents about the stakeholder group they belong to, their years of professional experience, and their level of seniority within their organisations. Second, the survey presented a series of options to measure a criteria given in the Spanish law, and asked respondents to state whether they agree/disagree that this option is appropriate for decisions about inclusion or non-inclusion of a medicine in the basic package of benefits of the NHS. Respondents were also given a 'free-text' option labelled as 'Other' where respondents could express views not captured in any of the options offered in the question. The third block asked respondents to indicate the weight (from 0 to 100) that they thought each criterion should have in the funding decisions for medicines in Spain, given that the sum of the scores should be 100. Fourth, we asked if respondents believed the criteria listed in the law are appropriate, and if they thought any additional criteria should be taken into account, particularly the patient perspective.

3.2 Statistical methods

Most questions in our survey allow for multiple responses, but some only allow one response, depending on whether we thought the responses were mutually exclusive or if decisions could be informed by alternative ways of measuring the same criteria. Annex IV shows which questions allowed multiple responses and which only allowed a single response.

To analyse the degree of association between the respondents' characteristics and their responses, logistic regressions were fitted to each question following equation (1):

$$y = \beta_1 institution + \beta_2 experience + \beta_3 position + \varepsilon$$

where y represents the respondent's binary choice to a specific question, and the categorical independent variables indicate the institution where the respondent works (Regional HTA agency, Spanish medicines regulatory agency, consulting firm, government institution/ministry of health, industry, academia, other), the years of experience in the field (<3, 3–5, 5–8, >8), and the position of the respondent (manager, technical, other). The coefficient indicates the degree of correlation between the probability of choosing each response and the independent variable. Independent variables with no coefficients are the reference category. A positive (negative) coefficient for a particular variable indicates a person in that category is, on average, more (less) likely to choose that response than a person in the reference category (see Annex V).

4. Results

4.1 The sample

We distributed the survey via email to the interest groups and professional societies, with collectively about 1000 members. We received 90 responses. The aim of the strategy we applied to distributing our survey was to reach a sample of individuals with the right skillset to respond to

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our survey that was as large as possible. No formal hypothesis or sample size calculation was applied.

The highest proportion of responders belonged to one of the HTA bodies that compose the RedETS (23 (26 per cent)). The second group most represented amongst respondents is governmental entities (15 (17 per cent)), including but not limited to the Spanish Ministry of Health (e.g. some of the members of AES could work for their regional departments of health and would fall under this category). The third most represented group in our survey were researchers (13 (14 per cent)), closely followed by industry representatives (13 per cent). Other groups included staff from regulatory agencies (10 (11 per cent)), hospital pharmacists (10 (11 per cent)), and consultants (7 (8 per cent)). Most (72(80 per cent)) had 8 or more years of experience.

4.2 General overview of preferred measurement instruments

Table 1 classifies responses in ranges of percentages of respondents who chose each one of the options we listed in the survey. Detailed responses to all questions in the survey are tabulated in Annex VI.

4.3 Severity, duration, and sequelae of the different pathologies for which they are indicated

As instruments to measure the baseline severity, duration, and sequelae of the different pathologies for which a new medicine is indicated, we offered respondents five options, allowing them to mark multiple ones (i.e. meaning that they believe more than one way of measuring this should be used to inform decisions). The most voted options, both voted by 61 (68 per cent) respondents, were: the QALY, and the use of clinical markers of severity, duration, and sequelae.

At a significance threshold of 5 per cent, the regression found that industry ($p = 0.022$) and technical staff ($p = 0.008$) were least likely to choose the QALY ($p = 0.022$) while academics were least likely to prefer clinical markers of baseline severity (see Table A1 in Annex V).

4.4 Specific needs of certain groups

Spanish legislation requires that the specific needs of certain groups are taken into account in reimbursement decisions in Spain, without naming particular groups or needs. We consulted our respondents about four groups: those with unmet medical needs, rare diseases, paediatric populations, and those at the end of life. Multiple responses were allowed. Most respondents thought patients with unmet need (82 (91 per cent)) and orphan medicines or rare diseases (64(71 per cent)) should have special consideration in reimbursement decisions. There was less support for giving special consideration in reimbursement decisions to paediatric populations (42 (47 per cent)) (Denburg *et al.*, 2020; Moretti *et al.*, 2022) and patients at the end of their life (32 (36 per cent)) (McCabe *et al.*, 2016).

Five (6 per cent) of respondents used the free-text box to express views not captured by any of the options offered in our survey. One of the respondents suggested in this section that any special consideration of any specific group should be based on empirical evidence of societal preferences, such as the large cross-sectional survey done by Linley and Hughes (2013) to elicit the views of the public around some of the special consideration the NICE gave to specific groups at that time (Linley and Hughes, 2013). Another expert suggested that situations where specific groups could be left in situations of social exclusion or other kinds of discrimination deserve particular attention. A different respondent suggested that the health care budget should simply follow burden of disease (measured in DALYs). A response indicated a view not captured amongst the options we offered to respondents, which was not to give special consideration to any of the groups we outlined in our survey. And finally, an expert suggested that we consider the possibility

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Table 1. Preferred ways of measuring each criterion ($N = 90$)

	0–25%	26–50%	51–75%	76–100%
Severity[a]	Disease-specific severity instrument (19 (21%)), Other (2 (2%))	DALY (40 (44%))	QALY (61 (68%)), Clinical units (61 (68%))	–
Specific groups[a]	Other (5 (6%))	Paediatric population (42 (47%)), End of life (32 (36%))	Rare diseases (64 (71%))	Unmet need (82 (91%))
Therapeutic value[a]	Other (0 (0%))	Clinical units (44 (49%)), Clinical benefit index – French approach (SMR) (44 (49%))	–	QALY (72 (80%))
Cost-effectiveness[a]	Other (6 (7%))	–	ICER (60 (67%))	ICUR (70 (78%))
Threshold (yes/no)	No (6 (7%))	–	–	Yes (84 (93%))
Threshold (explicit/implicit)	Implicit (14 (16%))	–	–	Explicit (70 (78%))
Threshold (special situations: yes/no)	No (10 (11%))	–	–	Yes (74 (82%))
Social value[a]	Other (4 (4%))	Impact of industry on the local/national economy (25 (28%))	–	QoL informal carers (73 (81%)), Productivity (87 (97%))
Budget impact	Pharmaceutical spending, 3–5 years horizon (3 (3%)), Other (9 (10%))	–	–	Total expenditure, 3–5 years horizon (78 (87%))
Therapeutic[a] alternatives	ATC4 (11 (12%)), Other (8 (9%))	ATC5 (34 (38%))	Therapeutic equivalent (59 (66%))	–
Degree of innovation[a]	Other (9 (10%))	MCDA (32 (36%))	Checklist (49 (54%))	–

[a]Respondents were able to choose one or more options in the survey.

of incorporating equity concerns in cost-effectiveness analysis, using the distributional cost-effectiveness analysis approach, which allows incorporating equity-relevant social considerations (such as, socioeconomic status, ethnicity, or location) and disease characteristics (like severity of illness, rarity, or disability) to the economic evaluation (Asaria *et al.*, 2016).

Academics were least likely to think that orphan designation deserves special consideration ($p = 0.049$) and technicians were least likely to select end of life for special consideration ($p = 0.046$) (see Table A2 in Annex V).

4.5 Therapeutic and social value of the medicine and its incremental clinical benefit, taking into account its cost-effectiveness

Health economists usually distinguish between a health service perspective for HTA, which considers therapeutic value and cost-effectiveness, and a societal perspective, which considers a wider set of outcomes. Hence, we formulated different questions to cover each one of these domains.

To measure the therapeutic value or the incremental clinical benefit of a new medicine we proposed a number of approaches, allowing multiple responses in our survey. The most voted measure was the QALY (72 (80 per cent)). About half of respondents thought clinical variables would be appropriate, and a similar number considered it would be appropriate to use a scale similar to the French approach to quantifying clinical value and clinical added value (Haute Autorité de Santé, 2014; Kergall *et al.*, 2021).

To measure the cost-effectiveness of the new therapy (compared to the standard of care) we gave two options, again allowing multiple responses, with most respondents tagging the incremental cost-utility ratio (ICUR) as their preferred approach (70 (78 per cent)) with the ICER as a close follower (60 (67 per cent)).

A cost-effectiveness threshold (CET) is a decision rule based on ICERs or ICURs (in the case of cost-utility thresholds (CUTs)) that distinguishes treatments that can be considered efficient use of resources from those that are not (Vallejo-Torres *et al.*, 2016). We asked in our survey if respondents thought a CUT was needed in Spain. A vast majority of respondents did deem it necessary (84 (93 per cent)). Out of that 93 per cent that deemed a threshold necessary, most preferred an explicit threshold (70 (78 per cent)) over an implicit one (14 (16 per cent)) (Schwarzer *et al.*, 2015). Within this group of respondents, 74 (82 per cent of the total sample) thought it appropriate to apply differential thresholds in particular situations or to particular population groups. Staff from the Spanish medicines regulator were less likely to favour incremental cost-utility analysis ($p = 0.004$) and the use of explicit CUT ($p = 0.003$) than respondents from regional HTA agencies (Tables A4 and A5 in Annex V).

The legislation also mentions the 'social value' of a medicine. We asked respondents to vote on proposed ways of measuring the social value, allowing them again to tag multiple responses if they thought that more than one way of measuring it should be accepted. The option deemed as an appropriate measure of the social value of a new medicine by the vast majority of respondents in our survey was the improvement in productivity, or in allowing earlier return to work, brought by the new therapy not only to the patient/s being treated, but also to those informally taking care of them (87 (97 per cent)). A metric that also received a high number of votes was a measure of the improvement in the quality of life of informal carers, in parallel with the amelioration of those they are caring for (i.e. the patient receiving the new therapy) (73 (81 per cent)). The option that attracted the least votes from respondents (25 (28 per cent)) was the consideration of the potential economic impact that the pharmaceutical company producing the new medicine could have on aspects of the national economy such as employment in the country, such as generating jobs for qualified personnel, and on other wider economic benefits (e.g. competitiveness, value added, etc.) (Weber, 2021).

Four additional respondents (4 per cent) opted for the 'Other' option, either to just highlight that they think other options would be best (without specifying which those should be),

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expressing alternative views to the ones offered in the pre-entered options, or complementing their responses using the free-text box.

4.6 Rationalisation of public spending on pharmaceuticals and budgetary impact on the NHS

Eighty-seven per cent of respondents believed that BIA should measure all health care costs (rather than just pharmaceutical sector costs). Staff of regulatory agencies were less likely ($p = 0.025$) than Regional HTA agency staff to wish to take into account costs to the wider NHS (beyond the cost of pharmaceuticals) (see Table A7 in Annex V).

Nine respondents (10 per cent) used the 'Others' option to express views not captured by any of the options offered in our survey. A respondent highlighted the need to scan the horizon for the specific medicine at hand, extending the time horizon up to the point of patent expiry if necessary, or up to timepoints when there would be any other kind of relevant landmark in terms of budget impact. A few respondents argued that time horizons longer than 5 years would be more appropriate.

4.7 Availability of medicines or other therapeutic alternatives for the same conditions at a lower price or lower treatment cost

Fifty-nine (66 per cent) indicated a methodology of 'therapeutic equivalence' would be appropriate to inform this criteria, 34 (38 per cent) opted for ATC5, and 11 (12 per cent) opted for ATC4. Multiple responses were allowed. Respondents working in regulatory agencies were less likely ($p = 0.033$) than Regional HTA staff to consider the ATC group 5 as representing equivalent alternatives (see Table A8 in Annex V).

Eight additional respondents (9 per cent) used the 'Others' option to express views not captured by any of the options offered in our survey. A responder suggested that the concept of equivalence is not appropriate here because it may include off-label uses. Another suggestion was to avoid using, in reimbursement decisions, instruments that have not been designed for such purpose since that could lead to unintended errors, such as neglecting potential differences in the pharmacodynamic and pharmacokinetic properties of a new galenic formulation.

4.8 Degree of innovation of the new medicine

In this category, multiple responses were not allowed, since we understood that applying more than one of the options we offered to measure the degree of innovation would incur in redundancy in practice, and it would not offer substantially enough additional information to support decisions to justify the duplicative effort. The most voted option was using a checklist to measure the degree of innovation (49 (54 per cent)). In this option, we offered the example of the checklist developed by the International Network of Agencies for Health Technology Assessment to support the development of HTA reports (Hailey, 2003), and clarified that such an instrument to purposely measure the degree of innovation for HTA purposes would need to be the subject of further research. Multi-criteria decision analysis (MCDA) was the alternative we offered, and received less votes (32 (36 per cent)).

Nine additional respondents (10 per cent) used the 'Others' option to express views not captured by any of the options offered in our survey.

4.9 Relative weights of criteria

We asked respondents to indicate the weight (from 0 to 100) that they think each criterion should have in the funding decisions for medicines in Spain, asking them to ensure that the sum of the

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scores given sums up to 100 (Table 2). On average, respondents thought therapeutic and social value should have the greatest weight, followed by severity.

4.10 Are we addressing all relevant criteria?

Less than half of respondents (44 per cent) thought the criteria in the law are adequate to support reimbursement decisions for medicines in Spain are adequate. Seventy-seven per cent thought other criteria should be added to the list, and 74 per cent thought that the perspective of patients should be considered as an additional criterion.

Respondents working in consulting firms and academic institutions were less likely to consider that the current criteria were adequate (see Table A.10 in Annex V).

5. Discussion

Decision makers in the health sector must allocate resources to make optimal use of limited health care budgets. Clearer, more predictable guidance about how price and reimbursement decisions are made and how developers should substantiate value propositions for new health technologies can promote more consistent and legitimate decision making, and ultimately, better outcomes for patients (Drummond *et al.*, 2008, 2022). In this paper, we illustrate the views of technical experts on how methodologies should be developed for reimbursement of medicines in Spain.

To measure severity, the respondents were in favour of using clinical units or the QALY. The use of clinical units is simpler and permits comparison of severity within a given disease. Estimating baseline QALY (as practiced in England and the Netherlands) usually requires a more complex modelling approach, but allows comparison of severity on a common basis across all populations.

Most respondents thought patients with unmet need and orphan medicines or rare diseases should have special consideration in reimbursement decisions. There was less support for special consideration for paediatric populations and patients at the end of their life.

Eighty per cent of respondents considered the QALY to be an appropriate measure of added therapeutic benefit. About half thought that clinical units or a grading system similar to the French ASMR could be used. The QALY as a universal measure of health is favoured by HTA bodies such as England and Sweden where cost-utility analysis carries a substantial weight in decision making. Notably, technical staff from the Spanish Medicines Agency (AEMPS) were less accepting of the QALY than those of regional HTA bodies. Similarly, while the majority of respondents favoured cost-utility analysis to measure efficiency, AEMPS technical staff were less likely to support these methods. This finding may provide an early indication that there are differences between the approaches favoured for medicines (which will be evaluated by AEMPS) and other health technologies (which will be evaluated by REDETS). This suggests further discussions, debate, and coordination may be needed to ensure a coherent and principled role for economic evaluation in Spain.

Most respondents were in favour of adopting an explicit CUT. A threshold for Spain has been estimated to be in the range of €22,000–25,000 per QALY (Vallejo-Torres *et al.*, 2018). The use of a CUT expressed as a 'cost-per-QALY' implies that health benefits must be measured using the QALY, which is something that has not yet been established in the Spanish system (Comité Asesor para la Financiación de la Prestación Farmacéutica del SNS (CAPF), 2022). Although methods guides are available (López-Bastida and Oliva, 2008; López Bastida *et al.*, 2010; Comité Asesor para la Financiación de la Prestación Farmacéutica del Sistema Nacional de Salud, 2023), use of economic evaluation is still piecemeal (Oliva-Moreno *et al.*, 2020, Vida *et al.*, 2023).

The value of a new medicine to society might go beyond what an ICUR would capture. There was very broad support amongst respondents to capture the impact of health care on productivity

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Table 2. Relative weights of reimbursement criteria (descriptions of criteria simplified for brevity)

Criterion	Average weight from all responses
Severity	21
Specific populations/needs	13
Therapeutic and social value, incremental benefit and cost-effectiveness	26
Budget impact	16
Availability of an equivalent alternative	14
Degree of innovation	10

and on informal carers. Interestingly, there was less enthusiasm for using the price and reimbursement of medicines to explicitly promote industrial policy.

Some countries, such as England, the Netherlands, and Norway, reward medicines that address the needs of particular patient groups by applying different thresholds for given populations (Pinto-Prades *et al.*, 2014). In general, payers across the biggest medicines markets in Europe appear to offer price premiums to medicines for rare diseases (Medic *et al.*, 2017). Alternatively, Danzon advocates for not implementing a higher threshold or premium price for orphan medicines, and instead dedicating future research to studying whether a higher value-based threshold could be granted for a subset of orphan indications which fulfil conditions of: (1) disproportionately high R&D costs per patient and; (2) can be subject to a limitation of indication expansions (to limit the potential negative impact on non-orphan indications that an overly stark shift of R&D towards orphan indications could cause) (Danzon, 2018).

The budget impact to the system was one of the criteria analysed in our survey. The options we offered as potential ways to capture the budget impact were very straightforward approaches to analysing the actual costs involved in implementing a new intervention. However, on top of measuring the actual economic impact of incorporating a new technology in the system, there are ways of embedding the budget impact in the reimbursement decision-making process that are relevant to consider. For instance, in England NICE introduced the so-called budget impact test in 2017, whereby NICE estimates the budget impact of all recommended medicines over the first 3 years of introduction in the system, and if the result is over the £20 million mark, pricing negotiations between the NHS and the sponsor are triggered (Ogden, 2017). Other countries such as Australia, Belgium, Ireland, France, Poland, Brazil, and Canada, also have official guidelines outlining the principles and methods that should underpin BIA in their systems, as well as the decision rules that might gravitate around them (Foroutan *et al.*, 2018). Further elaboration of how budget impact is calculated and used to inform financing decisions for medicines in Spain would match the Spanish system with international comparable health care systems.

The Spanish legislation requires that new medicines should be offered at a lower price or cost in areas where there are existing therapeutic alternatives, which begs the question of what is meant by 'therapeutic alternative' in this context. Using the concept of 'therapeutic equivalence' (Cappello *et al.*, 2020) to substantiate P&R decisions received the highest number of votes in our survey (59 (66 per cent)). The ATC groups 5 and 4 received less attention from respondents (34 (38 per cent) and 11 (12 per cent) respectively). Indeed, the WHO does not recommend using the ATC system for P&R decisions (WHO Collaborating Centre for Drug Statistics Methodology, 2022). This shows that combining clinical and economic considerations to inform P&R decisions is a complex task, and suggests further methodological development is needed to define the concept of therapeutic alternative in the context of pricing decisions.

The degree of innovation is the last criteria, though it is rarely invoked in practice (Ministerio de Sanidad, 2024a). Providing a clear definition of what is understood by degree of innovation in

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Table 3. Key issues and recommendations

As a measure of health in economic evaluations, survey participants recommended the QALY, and the use of an explicit CUT that can vary to give particular consideration to specific patient groups or therapies, such as those responding to previously unmet medical needs. Participants were in favour of measuring baseline severity by clinical units or by QALY.
Survey participants recommended that budget impact should be capturing all costs relevant to the health care system within a 3–5 years horizon. Further elaboration of how budget impact should be calculated and its place in informing financing decisions for medicines in Spain would be welcomed.
Survey participants recommended the development of a concept of 'therapeutic equivalence' to capture situations where the new medicine is no better than an existing alternative. This would require AEMPS to define this concept.
Survey participants recommended the development of a checklist to capture the degree of innovation offered by a new medicine. This instrument would add robustness and transparency to the P&R process.
Survey participants recommended capturing the patients' perspective in a systematic and robust manner to support reimbursement decisions for medicines in Spain. This aligns with current plans for HTA development in Spain.
A large study to elicit the preferences of the Spanish society around which groups deserve particular consideration in medicines financing decisions would be very useful to inform policy making in this area.
Duplication should be avoided when rewarding specific dimensions of value of health technologies (e.g. adding price premiums to a therapy twice – once for rarity and once for severity). National decision makers should take into account the incentives provided by the new European pharmaceutical regulation when considering whether these products should also qualify for premium prices in NHSs.

the context of reimbursement decisions in Spain, and how to measure it, would add robustness and transparency to the process.

The preferred way of measuring the degree of innovation of a new medicine was the use of a purposely designed checklist. This should be the subject of further regulatory development. There was less support for MCDA. This method has its proponents and critics. Some argue that it is overly mechanistic (Baltussen *et al.*, 2019), while others highlight the potential of this approach but still see plenty of scope for methods development (Thokala and Duenas, 2012; Marsh *et al.*, 2018).

A majority of experts supported the inclusion of the patients' perspective as an additional criterion, which is in line with ongoing reforms in Spain aiming to incorporate representatives of patient groups into decision-making processes (Angulo Romero *et al.*, 2022).

The criteria weighting exercise we carried out amongst the respondents shows that, for them, the most important criteria when deciding whether or not a new medicine should be reimbursed is its therapeutic and social value and its incremental clinical benefit, taking into account its cost-effectiveness, as well as the severity, duration, and sequelae of the different pathologies for which it is indicated, both with weightings of more than 20 out of 100.

Additional areas for further research were indicated by respondents. One mentioned the need to incorporate equity concerns in cost-effectiveness analysis (Asaria *et al.*, 2016; Vallejo-Torres, 2023). Another respondent argued that societal preferences, rather than experts, should decide broad priorities for health service decisions. This suggests the need for increased public participation in decision making and the undertaking of larger societal preference studies (Clark and Weale, 2012; Linley and Hughes, 2013; Costa-Font *et al.*, 2015). This could be a useful line for further research in the Spanish context.

Spain implemented a reform in 2021 to create the Pharmaceutical Evaluation Network (REvalMed), which combined clinical and economic evaluation in a single collaborative structure (Arganda, 2023). However, the legal and organisational ambiguities in this structure were strongly criticised (Vida *et al.*, 2023), and in 2023 the High Court ruled that it could not continue. Additionally, countries in the EU must adapt to the new European regulation on HTA (Proposal for a Directive of the European Parliament and of the Council, 2023). As a response to these challenges, the Spanish Ministry of Health officially announced in October 2023 the

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launch of a process to reform the law regulating the architecture of the Spanish HTA system (Ministerio de Sanidad, 2024b), and another new law is expected that reforms the regulation governing P&R of medicines and other health technology. The main issues raised in this paper are summarised in Table 3 and may be relevant to the design of the new HTA and P&R systems.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S174413312400029X.

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