This is a "preproof" accepted article for *International Journal of Technology Assessment in Health Care*.
This version may be subject to change during the production process.
DOI: 10.1017/S0266462325100226

STAKEHOLDER SURVEY ABOUT BROAD ELEMENTS OF VALUE IN HEALTH TECHNOLOGY ASSESSMENT IN AUSTRALIA: INDUSTRY AND ACADEMIA MORE SIMILAR THAN DIFFERENT

Running heading: Survey of broad value elements in HTA in Australia

Maria Farris BSc

Astra Zeneca, Macquarie Park, Australia.

Stephen Goodall PhD

Centre for Health Economic Research and Evaluation,

University of Technology Sydney, Australia

Richard De Abreu Lourenco PhD

Centre for Health Economic Research and Evaluation,

University of Technology Sydney, Australia

Correspondence: Maria Farris, Centre for Health Economic Research and Evaluation, University of Technology Sydney, Sydney, Australia Email:Maria.H.Kokoszka@student.uts.edu.au

Abstract

Objective

Researchers propose wider individual and societal benefits (or broad elements of value) be included in economic evaluations (EEs) of medicines. This study investigates opinions of Australian stakeholders regarding the inclusion of broader value elements in reimbursement decisions for medicines for rare diseases in Australia.

Method

Stakeholders were invited via email to complete an online survey about their views on broader elements of value in HTA. Responses were summarised using descriptive statistics and compared using chi-square statistics.

Results

Forty-four respondents (academia (n=11), private sector (n=33)) completed the survey between October 2023 and May 2024. Only 27percent of stakeholders agree the current information about the sources of value considered in reimbursement decisions is sufficient. Stakeholders consistently agree labour productivity (>50percent), adherence (>80percent), reducing uncertainty due to a new diagnostic (>70percent), disease severity (>71percent), value to caregivers (>70percent), and equity (>70percent) should be considered in HTA. The majority (>70percent) agreed managed entry agreements (MEA), risk share arrangements (RSA), and multi criteria decision analysis (MCDA) be used in reimbursement decision making for medicines for rare diseases. Significantly fewer academic stakeholders (40percent) versus private sector (77percent), believe an increased willingness-to-pay threshold be applied to medicines for rare disease.

Conclusions

Academic and private sector stakeholders hold similar views when considering medicines for non-rare and rare diseases. Stakeholders favour considering more value elements in HTA than referred to in the Pharmaceutical Benefits Advisory Committee (PBAC) guidelines. This study highlights further advice is needed on the factors considered in reimbursement decisions and how that would influence guidelines.

https://doi.org/10.1017/S0266462325100226 Published online by Cambridge University Press

Keywords

- Rare Diseases
- Uncertainty
- Advisory Committees
- Technology Assessment, Biomedical

Introduction

Economic evaluation (EE) is widely used in health technology assessment (HTA) to inform reimbursement decisions in healthcare[1, 2]. As part of HTA, an EE assesses the incremental cost-effectiveness (CE) of a new therapy and the incremental cost-effectiveness ratio (ICER) is judged against an implicit or explicit "cost-effectiveness threshold," to help judge the efficient allocation of healthcare resources[3].

EE's can only include benefits for which adequate data is generated[4]. Typically only direct patient health benefits via quality of life (QoL) and survival (used to calculate quality-adjusted life years [QALYs]) are considered in an EE [5]. They can however adopt a wider, societal perspective and incorporate broader elements of value such as indirect non health benefits offered by a medicine [6-8]. The perspective taken by decision makers is often outlined by HTA guidelines reflecting their country values and preferences, and they may be required to consider a government perspective only rather than the societal perspective[1, 5].

Several studies suggest wider benefits to individuals and society should be included in EE's [9-11]. An International Society for Pharmacoeconomics and Outcomes Research (ISPOR) special task force on value assessment recommend a series of broader value elements in HTA assessments [9]. Because if HTA does not include the broader value of a therapy then treatments with wide ranging impacts may be undervalued and receive inappropriately high ICERs [8, 12]. Some of the broad value elements suggested range from conventional concepts, such as adherence improving factors or disease severity, to novel elements of value such as scientific spillover[9].

Rare diseases are a group of diverse diseases, characterised by low prevalence and often have severely debilitating symptoms that substantially affect the QoL of patients and their families [13, 14]. EEs of medicines

for rare diseases often produce high and uncertain ICERs, in part due to their high cost and difficulty generating robust evidence supporting clinical efficacy due to small sample sizes, single arm studies, shorter duration of patient follow up and reliance on immature clinical evidence to inform modelling [3, 13]. Different reimbursement agencies provide varying recommendations based on EE's of the same medicine for rare disease, partly because factors like disease severity and indirect treatment benefits were considered, leading to greater acceptance of higher and uncertain ICERs [15, 16]. Additionally, some rare disease medicines have gained expedited access in cases of high unmet need through payment mechanisms like outcome-based managed entry agreements (MEA's) to address the financial risks associated with uncertain clinical evidence [17].

To improve the quality of EE's, experts recommend an impact inventory to explicitly consider the broader health and non-health impacts of a medicine[7]. Because methods to include broad value elements into value assessment are unclear HTA agencies use different approaches [18-20]. Two mechanisms to formally include broader elements of value into an EE are a multi criteria decision analysis (MCDA), or the deliberative process[21]. The latter is used by reimbursement agencies such as the National Institute for Health and Care Excellence (NICE) in England and Wales and the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia. However, deliberative processes have their shortcomings as the relative importance of various criteria varies between stakeholders, which elements of value contributed to the decision is not always clear and how the decision was reached is not always transparent [13, 21-25].

This study investigates the opinions of Australian stakeholders in the HTA process about the importance of various broader elements of value in EEs, transparency in reimbursement decision making in Australia, and opinions on mechanisms to manage uncertainty associated with medicines of rare diseases.

Methods

A quantitative survey was conducted of stakeholders involved in HTA in Australia, representing academia, specialist consultants and the pharmaceutical industry. An invitation was emailed to potential participants (including government agencies and representatives of patient organisations) via local professional societies and invitees were encouraged to forward the survey to other relevant colleagues. No responses from government agencies and patient representatives were received.

The survey was developed using the Qualtrics Survey platform and was completed between 02 October 2023 and 14 May 2024. Questions were based on the broader elements of value proposed by ISPOR and mechanisms suggested, and adopted, to manage uncertainty in value assessment [9, 23, 24, 26]. The questions were discussed

https://doi.org/10.1017/S0266462325100226 Published online by Cambridge University Press

with a expert health economists experienced in HTA prior to implementation. Prior to initiation of the survey, the appropriateness and order of the questions were discussed within the research team. Pilot testing of the survey was conducted with internal and external members of the research team to assess comprehension. The survey comprised 32 questions across six sections (Supplement S1) and was intended to take approximately 10 minutes to complete.

Because value elements are sometimes referred to by other names in the literature or the names may not represent the essence of what is considered, a brief description of each 'value element' was included in the survey. A description of the broader elements of value and mechanisms to manage uncertainty in value assessment that were presented in the survey are presented in Table 1.

Table 1 Description of the broader elements of value and mechanisms to manage uncertainty in value assessment presented in the survey

Most questions sought agreement to statements on a 5-point Likert scale: 1=strongly disagree, 2=somewhat disagree, 3=neither disagree nor agree, 4=somewhat agree, 5=strongly agree (respondents could choose a sixth category 'Don't know'). Depending on the resulting number of respondents, and to ensure >5 minimum responses per category (for statistical testing), the categories ‘strongly agree’ and ‘somewhat agree’ were collapsed into one group ('Agree'), and the categories ‘strongly disagree’ and ‘somewhat disagree’ into another group ('Disagree'). The category ‘neither disagree nor agree’ or “don’t know” is henceforth referred to as ‘neither’ within the text. The remaining questions asked participants whether they agreed with statements with response options 'yes', 'no' or 'not sure', and to nominate methods (via a free text field) to incorporate added value not currently utilised in EE’s. If the response was 'yes' the participant was reported to 'Agree'. A response “No” or “Not Sure” reflected that the participant did Not Agree with the statement

Five major categories of stakeholders were defined for respondents to self-allocate 1) pharmaceutical industry, 2) specialist consultants, 3) academia, 4) government agency and 5) representative of patient organization. Within the Australian HTA process, academia is responsible for the independent evaluation of reimbursement applications. Specialist consultants, typically HTA consultancy firms, are engaged by the pharmaceutical industry to assist in the preparation of these applications. Responses to each question were summarised using descriptive statistics and reported for the cohort overall and by respondent categories separately. Test for difference between respondent categories were performed using chi-square statistics (5percent significance

https://doi.org/10.1017/S0266462325100226 Published online by Cambridge University Press

level). The relative risk (RR) (academic group versus Private sector groups) and 95percent confidence interval (CI) are estimated for each response.

Where no background demographics were reported for a participant who consented, their data was removed from the sample. If demographic data were reported but only partial survey response data was provided, participant responses were only included in those questions to which they contributed (thus the sample size varies per question).

All analyses were performed using Excel on a MS Windows platform.

This study received ethics approval in September 2023 (HREC REF NO. ETH21-6090).

Results

Forty-four respondents completed the survey from academia (n=11) and the private sector (n=33). The respondent categories were aggregated into 'academia' and the 'private sector' (pharmaceutical industry and specialist consultants). The sample was adjusted by excluding three respondents without demographic data. The majority of respondents in both groups had a post graduate degree (Masters 27/44, 61percent or Doctoral 14/44, 32percent) and the top three primary qualifications were in health economics (28/44, 64percent), pharmacy (11/44, 25percent) and science (10/44, 23percent). Mean (standard deviation, SD) years of experience was 7.3 years in academia and 14.3 years in the private sector (Table 2). Most (67percent) in private sector held managerial roles compared with only 18percent (2/11) of the academic group.

Table 2 Background information for all stakeholders and by subgroup

Few (<30percent) Australian stakeholders agree that the current HTA methods applied in Australia are adequate to appropriately assess the CE of all medicines or medicines for rare disease (Table 3). Despite the absence of a significant difference in responses between stakeholders, it is noteworthy that academic respondents were four times more likely (RR 4.36) to agree that the HTA methods used in Australia are adequate for all medicines, compared to their private sector counterparts. However, the substantial uncertainty surrounding this estimate is reflected in the wide confidence interval (range 0.84 to 22.79). The majority of stakeholders disagreed with the statement that the public information on reimbursement decisions in Australia provides sufficient information about which sources of value are considered and how they contributed to decision making (73percent; academia=55percent versus private sector=80percent, p=0.1031) (Table 3). It is important to emphasize the

https://doi.org/10.1017/S0266462325100226 Published online by Cambridge University Press

variation in response rates, despite the lack of statistical significance. Notably, academics were twice as likely (RR 2.27) to concur that the publicly available information on reimbursement decisions is adequate compared with the private sector. Of the 24 respondents from the private sector who disagreed, 83percent felt that while they knew which sources of value were considered, they did not know how they contribute to decision making. Equal proportions of respondents from academia thought that either the sources of value considered were not known (33percent) or did not know how they contributed to decision making (33percent).

The majority of stakeholders (70percent; academic=50percent versus private sector=77percent, p=0.1110) agreed that having an explicit checklist on additional value considered beyond the QALY by decision makers would be more informative than what is currently published in Australia (Table 3). There is an imbalance in responses however, a RR of 0.65 suggests that the academic group were 35percent less likely to agree than private sector stakeholders that a checklist may be more informative. Importantly, the 95percent CI range (0.34 to 1.25) indicates uncertain precision of this effect.

Stakeholders were invited to explore mechanisms to facilitate expedited access to treatments for rare diseases, while effectively managing the uncertainties associated with cost-effectiveness analysis (CEA) and budgetary impacts (BI). This consideration is driven by the significant unmet need and the demand for accelerated access to such medicines.

Most Australian stakeholders (>68percent) agreed the four mechanisms (MEA's, financial risk share arrangements [RSA's], MCDA's and increased ICER's considered acceptable for treatments of rare diseases denoted as willingness to pay [WTP]), should be used in making reimbursement decisions about medicines for rare disease (Table 3). Over seventy percent (>70percent) of academia and private sector respondents agreed that MEA's RSA's and MCDA should be used in making reimbursement decisions for medicines for rare disease in Australia (Table 3). Significantly fewer academic respondents (40percent) compared with the majority of private sector respondents (77percent) (p=0.0320) agreed that an increase in the ICER considered acceptable for medicines for rare diseases in Australia, should be used in decision making.

Table 3 Comparison of methods to assess cost-effectiveness in HTA for all medicines and medicines for rare disease, public information regarding the sources of value and mechanisms for decision making in medicines for rare disease

https://doi.org/10.1017/S0266462325100226 Published online by Cambridge University Press

The majority of all Australian stakeholders (>65percent) believed that six of the eleven broader value elements recommended by ISPOR: labour productivity, adherence, reducing uncertainty due to a new diagnostic, severity of disease, value to caregivers, and equity should be considered in HTA of all medicines and medicines for rare disease (Table 4). Whereas few stakeholders agreed that the value of hope, real option value, scientific spillover, fear of contagion or insurance value should be considered (Table 4).

The degree of consensus between the stakeholder groups is demonstrated by a RR close to 1.0 accompanied by a narrow confidence interval. This indicates consensus between academia and private sector respondents on the majority of broader value elements agreed should be considered in HTA of all medicines and medicines for rare disease in Australia, namely adherence, reducing uncertainty due to a new diagnostic, severity of disease, and equity. Furthermore, the analysis revealed no statistically significant differences in responses when analysed by sector (Table 4). Interestingly the likelihood of agreeing to include "Labour Productivity" in HTA of all medicines and medicines for rare disease in Australia is approximately 30percent less in the academic respondents compared with private sector respondents. Also, the likelihood of the academic group agreeing to include "Value to caregivers" in HTA of medicines for rare disease in Australia (RR0.75) is 25percent less likely than the private sector, yet the degree of concordance was greater when considering HTA of all medicines (RR0.86). In addition the majority of both stakeholder groups did not agree that the Value of Hope should be considered in HTA of all medicines and medicines for rare disease in Australia (<43percent), the likelihood of agreeing that it should be included was 50percent lower in the academic respondents compared with private sector respondents (RR 0.46 and RR0.38, respectively). Each group was aware of methods to capture impacts on costs and outcomes for the broad sources of value, such as quality of life measures, subgroup analysis and distributional cost-effectiveness analysis (DCEA) (Table 5).Table 4 Comparison between sources of value that should be considered in HTA for all medicines and medicines for rare disease

Table 5 Comparison between stakeholder groups regarding sources of value that should be considered in HTA for all medicines and suggested methods to include them into EE's

Discussion

https://doi.org/10.1017/S0266462325100226 Published online by Cambridge University Press

This study examined views from academic and private sector stakeholders involved in HTA on which broad elements of value should be considered by decision makers in Australia, and mechanisms to mitigate uncertain CE and BI associated with medicines for rare diseases.

The majority of respondents agreed that current public information regarding reimbursement decisions in Australia provides insufficient information about the consideration of sources of value in decision-making. Furthermore, the majority of respondents agreed that current HTA methods applied in Australia are inadequate to appropriately assess the CE of all medicines and medicines for rare disease. Australian reimbursement recommendations are made transparent to the public by publishing them online as public summary documents (PSDs) [29]. They provide contextual information pertaining to each recommendation and although they are limited in terms of the amount of information published, they provide insight into the factors and trade-offs noted through the deliberative process in arriving at reimbursement recommendations [30]. Transparency on which inputs are accepted (and under what conditions) by HTA decision makers is necessary because it enables stakeholders to collect relevant data to inform decision making [31] This study highlights transparency on what was considered in PBAC decision making in the PSD needs further improvement. Of interest, participants in Australia's recent HTA policies and methods review (referred to as the "HTA review") expressed concern that PSDs fail to adequately convey how certain evidence types impact health technology funding decisions [28]. The HTA review findings are consistent with those from this survey.

More private sector stakeholders (77percent) than academic stakeholders (50percent) thought an explicit checklist of sources of value beyond the QALY, and information on whether they were considered by a decision maker, would be more informative than what is currently published in Australia. Private sector stakeholders, particularly those in the pharmaceutical industry, may have more interest in PBAC decision-making than academics, as they depend on these decisions for medication funding (Table 1). Nonetheless, experts suggest a checklist for reimbursement decision making as a useful framework to standardize the consideration of sources of value,minimize bias and improve transparency [7,9,18,32]. The HTA review recommends that the Australian Government develop and support an explicit qualitative values framework to ensure HTA decisions consider broader value, enhancing transparency and consistency in funding health technologies [28]. Importantly the recommendation states the framework should allow enough flexibility for the deliberation process itself to add value that is not pre-weighted and scored. Examples of explicit qualitative value frameworks and transparent reporting by HTA committees include the Institute for Clinical and Economic Review (I.C.E.R.) in the US that refers to "Potential other benefits and contextual considerations" such as health disparities, caregiver burden, or

impact the entire “infrastructure” of care that committee members individually rate during deliberation [27]. The I.C.E.R value framework is systematic regarding the factors incorporated into decision making and explicitly reported [29]. NICE includes non-quantified additional health benefits such as to the health system (e.g. equity), and innovation [25]. The NICE final outcome describes how such “other factors” impacted decision-making [30].

Less than 20percent of Australian stakeholders agree that fear of contagion and insurance value should be considered in HTA of all medicines or medicines for rare disease in Australia. Six broad value elements that most Australian stakeholder felt should be considered in HTA of medicines in Australia (labour productivity, adherence, reducing uncertainty due to a new diagnostic, severity of disease, value to caregivers, and equity) are recommended in several HTA guidelines whereas only two (severity of disease and equity) overlap with the 'less -readily quantifiable' factors quoted to “influence” PBAC decision making in Australia [5,33]. The PBAC guidelines highlight several factors considered during PBAC deliberations, such as the overall confidence in the evidence and assumptions presented, equity, severity, the capacity to target therapy, the existence of effective therapeutic alternatives, public health considerations, and any other pertinent factor influencing a medicine's suitability for listing on the PBS. These qualitative assessments, along with CE and BI, may obscure the weight of each factor in reimbursement decisions. Additionally, while the guidelines assert that "Supplementary analyses may be appropriate where the proposed intervention has important societal implications"—thereby permitting the inclusion of broader values in supplementary CEA—the relegation of non-health benefits to supplementary analyses might result in them being overlooked in the decision-making process and omitted from the PSD.

A recent review of 53 HTA guidelines representing 52 countries revealed an average of 5.9 of a possible twenty-one societal and novel value elements were mentioned although the authors acknowledge simply recommending novel elements of value in HTA guidelines may not lead to them being incorporated into decision-making [5]. Australian HTA guidelines outline a preferred approach for PBAC submissions but allow alternative approaches if justified with data. Stakeholders can include alternative value elements in submissions, but decision-makers must transparently evaluate these. Transparency is crucial for sponsors, as developing evidence is resource-intensive and can guide future evidence generation. Including well-supported broader value elements in decision-making acknowledges therapy benefits and aids patient access to medicines [15,16,19].

https://doi.org/10.1017/S0266462325100226 Published online by Cambridge University Press

There are challenges quantifying some broad value elements, and a lack of consistent methodology for their inclusion in EE's as well as expertise in assessing the methodologic approaches [5,8,9]. Both stakeholder groups were generally aware of methods to incorporate agreed-upon value elements into HTA of medicines. However, some elements like fear of contagion and insurance value lacked acknowledged methods. Suggested methods, within the CE framework, included preference-based methods, scenario analysis, and DCEA. Academics had higher method knowledge, indicating varying skill sets among stakeholders. This underscores the need for PBAC guidelines to provide guidance on data and methods to support broader value elements, alongside improving transparency in decision-making. For example, the Medical Services Advisory Committee (MSAC) in Australia includes the 'value of knowing' as a less quantifiable factor influencing decisions and offer technical guidance on evidence to support this element [34].

The inquiry into proposed decision-making mechanisms for reimbursing medicines for rare disease in Australia was framed by the context that medicines for rare disease are generally expensive with limited evidence of clinical effectiveness, attributed to small, non-comparative clinical studies and lack of epidemiological data. RSA's and outcome based MEA's are existing mechanisms employed in Australia to subsize medicines despite the lack of confidence in the evidence for a medicine [26]. Most stakeholders agreed RSA's and MEA's should be used in making reimbursement decisions about medicines for rare diseases. RSA's described in this study are a practical financial arrangement that continues to subsidise a medicine only when treated patients meet specific clinical criteria, it also provides certainty around financial expenditure to the government despite patient population size uncertainty. Outcome based MEA's are challenging to implement in Australia due to the absence of infrastructure linking medicine utilisation and clinical outcomes, and thus most MEA's implemented in Australia to date are limited to reviewing the recommendation to reimburse a medicine once additional outcome data becomes available from a clinical trial that is underway [26, 35, 36]. If MEA's are to be used to expedite access to medicines for rare diseases in Australia despite uncertain clinical evidence, handling challenges such as establishing infrastructure to support comprehensive data collection as well as price adjustments based on outcomes arrangements or product delisting due to suboptimal performance are some of the significant tasks for both payers and the pharmaceutical industry [26,37].

The MCDA method referred to in this survey was a quantitative MCDA whereby stakeholder preferences are used to specify a value for each criterion, the values are weighted, and an overall score generated for each intervention [21]. The use of quantitative MCDA in HTA is not widespread but most Australian stakeholders responding to the survey believe it should be used to make reimbursement decisions about medicines for rare

diseases in Australia [31]. The formal structure of MCDA, avoids some of the issues in less structured deliberative processes, explicitly elicits decision makers preferences and allows for the inclusion of broader value elements important to stakeholders but not easily accommodated in standard CEA's [21, 24, 38]. Two systematic reviews of quantitative MCDA found it useful for focusing discussion and reporting decisions transparently but found no evidence of improved decision-making quality or timeliness [32, 33]. Importantly, weighting of the relative importance of various value elements would likely differ between stakeholders such as patients and payers [21]. Consequently, the HTA review recommendation to develop a "qualitative value framework" that is neither pre-weighted nor pre-scored.

There was significant disagreement between the stakeholder groups regarding increasing WTP thresholds in making reimbursement decisions about medicines for rare disease. Among the many countries that use CEs to inform funding decisions (such as England and Wales, Australia, New Zealand, Canada, Sweden, the Netherlands, and others), only England and Wales, and the Netherlands use an explicit WTP threshold to make funding recommendations [39]. The PBAC do not explicitly report a fixed WTP value to judge the acceptability of a medicine as CE, but revealed and stated preference studies of PBAC decision making shows a preference for smaller ICERs to recommend a medicine [40, 41]. The view from academic stakeholders aligns with surveys of the Australian general public which shows there is no WTP a premium for rarity although there is a case for paying more for drugs that treat severe conditions, or where there is no alternative treatment available [42-44]. Nonetheless the PBAC have stated their willingness to accept a higher ICER in the face of significant uncertainty in the CE of a medicine for a rare disease [35].

A limitation of our study is the small sample size in this survey, and the unequal group sizes (academia, N=11; private sector, N=33). The timing of the survey, conducted during the recent HTA review in Australia, may have influenced participation, as stakeholders could have experienced fatigue due to the extensive feedback collection during the review. Discrepancies in sample sizes may account for the lack of significant differences observed, as smaller samples increase variability and standard error, reducing estimate reliability and sensitivity to detect differences. Additionally, recruitment through email and professional societies may introduce selection bias, as it depends on self-selection by more engaged stakeholders. Nevertheless, the participants had considerable expertise, averaging between 7-14 years of HTA experience, predominantly with health economic qualifications (Table 1), making their opinions likely a reliable reflection of other health economists in Australia. The absence of data from critical groups, such as government policymakers and patient representatives, limits the generalizability of our findings. Further research to include insights from these groups

and expand the sample size would be beneficial. There may be other value elements that stakeholders think should be considered in HTA of medicines in Australia beyond what was considered in this survey. Nevertheless, the broad value elements in the survey covers a wide range of value from societal elements (health impacts beyond the treated individual and costs beyond the healthcare sector such as productivity and scientific spillover), to novel elements (e.g., insurance value, fear of contagion and value of hope). Regardless, the list of broad elements of value are not intended to be final preferences of stakeholders.

Conclusion

The perspectives of Australian stakeholders in both the academic and private sectors were largely congruent, showing no statistically significant differences in views about the adequacy of current methods to assess the cost-effectiveness of all medicines and medicines for rare diseases. Stakeholders from both sectors involved in HTA in Australia expressed concerns that current HTA methods in Australia are inadequate for assessing the broader value of medicines. The private sector was particularly concerned that public statements about the funding of medicines lack transparency regarding which specific value sources influenced reimbursement decisions.

There was consensus among both groups favouring the inclusion of more value elements in HTA decision-making than currently recognized in the PBAC guidelines, specifically advocating for the integration of six out of the eleven values from the ISPOR value framework.

The survey's findings offer valuable insights relevant to the Australian HTA review's recommendations, suggesting an explicit qualitative framework be developed, informed by public consultation and existing research. Additional research to gather perspectives from patients and decision-makers and to increase the sample size would be advantageous. This study underscores the necessity for enhanced guidance in reimbursement guidelines and for greater transparency in the publication of decisions related to the values influencing decision-making.

https://doi.org/10.1017/S0266462325100226 Published online by Cambridge University Press

Acknowledgements and Sources of funding

Funding/Support/affiliations: This research was conducted as part of an industry Doctorate at the Centre for Health Economic Research and Evaluation (CHERE), University of Technology Sydney, Sydney, Australia, in partnership with AstraZeneca Australia. AstraZeneca Australia provides a Research Support Fee. Mrs Farris receives a salary from AstraZeneca.

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection , management, analysis, and interpretation of the data; or preparation of the manuscript. The manuscript was reviewed by AstraZeneca prior to submitting for publication. The views expressed are those of the authors and not necessarily those of AstraZeneca or the Centre for Health Economic Research and Evaluation (CHERE).

Conflicts of Interest: Mrs Farris is an employee of AstraZeneca Australia. No other financial or non-financial interests were reported by Maria Farris. Stephen Goodall and Richard De Abreu Lourenco have no relevant financial or non-financial interests to disclose.

Ethics approval: This study was approved for conduct under the Centre for Health Economic Research and Evaluation program ethics approval from the University of Technology Sydney Ethics Committee on September 2023 (UTS HREC REF NO. ETH21-6090).

Availability of data and material: Data used in this study can be shared upon reasonable request to the corresponding author.

Author Contributions:

Concept and Design: Farris, Goodall, De Abreu Lourenco

Acquisition of data: Farris

Analysis and interpretation of data: Farris

Drafting of manuscript: Farris, Goodall, De Abreu Lourenco

Supervision: Goodall, De Abreu Lourenco

Bibliography

1. Drummond MF, Sculpher, M.J., Claxton, K., Stoddart, G.L., Torrance, G.W. . Methods for the Economic Evaluation of Health Care Programmes. Fourth Edition ed: Oxford University Press; 2015 2015.
2. Garrison LP, Towse A. Value-Based Pricing and Reimbursement in Personalised Healthcare: Introduction to the Basic Health Economics. J Pers Med. 2017;7(3).
3. Drummond MF, Wilson DA, Kanavos P, Ubel P, Rovira J. Assessing the economic challenges posed by orphan drugs. Int J Technol Assess Health Care. 2007;23(1):36-42.
4. Stephens J. International survey of methods used in health technology assessment (HTA): does practice meet the principles proposed for good research? Comparative Effectiveness Research 2012(2):29-44.
5. Breslau RM, Cohen JT, Diaz J, Malcolm B, Neumann PJ. A review of HTA guidelines on societal and novel value elements. Int J Technol Assess Health Care. 2023;39(1):e31.
6. Al-Janabi H, van Exel J, Brouwer W, Coast J. A Framework for Including Family Health Spillovers in Economic Evaluation. Med Decis Making. 2016;36(2):176-86.
7. Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. JAMA. 2016;316(10):1093-103.
8. Scope A, Bhadhuri A, Pennington B. Systematic Review of Cost-Utility Analyses That Have Included Carer and Family Member Health-Related Quality of Life. Value Health. 2022;25(9):1644-53.
9. Lakdawalla DN, Doshi JA, Garrison LP, Jr., Phelps CE, Basu A, Danzon PM. Defining Elements of Value in Health Care-A Health Economics Approach: An ISPOR Special Task Force Report [3]. Value Health. 2018;21(2):131-9.
10. Garrison LP, Pezalla E, Towse A, Yang H, Faust E, Wu EQ, et al. Hemophilia Gene Therapy Value Assessment: Methodological Challenges and Recommendations. Value Health. 2021;24(11):1628-33.
11. Engel L, Bryan S, Whitehurst DGT. Conceptualising 'Benefits Beyond Health' in the Context of the Quality-Adjusted Life-Year: A Critical Interpretive Synthesis. Pharmacoeconomics. 2021;39(12):1383-95.
12. Shafrin J, Dennen S, Pednekar P, Birch K, Bhor M, Kanter J, et al. For which diseases do broader value elements matter most? An evaluation across 20 ICER evidence reports. J Manag Care Spec Pharm. 2021;27(5):650-9.
13. Nicod E, Annemans L, Bucsics A, Lee A, Upadhyaya S, Facey K. HTA programme response to the challenges of dealing with orphan medicinal products: Process evaluation in selected European countries. Health Policy. 2019;123(2):140-51.
14. Wu Y, Al-Janabi H, Mallett A, Quinlan C, Scheffer IE, Howell KB, et al. Parental health spillover effects of paediatric rare genetic conditions. Qual Life Res. 2020;29(9):2445-54.
15. Nicod E. Why do health technology assessment coverage recommendations for the same drugs differ across settings? Applying a mixed methods framework to systematically compare orphan drug decisions in four European countries. Eur J Health Econ. 2017;18(6):715-30.
16. Farris M, Goodall S, De Abreu Lourenco R. A systematic review of economic evaluations for RPE65-mediated inherited retinal disease including HTA assessment of broader value. Int J Technol Assess Health Care. 2023;39(1):e38.
17. Qiu T, Pochopien M, Hanna E, Liang S, Wang Y, Han R, et al. Challenges in the market access of regenerative medicines, and implications for manufacturers and decision-makers: a systematic review. Regen Med. 2022;17(3):119-39.
18. Drummond MF, Neumann PJ, Sullivan SD, Fricke FU, Tunis S, Dabbous O, et al. Analytic Considerations in Applying a General Economic Evaluation Reference Case to Gene Therapy. Value Health. 2019;22(6):661-8.

19. McQueen RB, Inotai A, Zemplenyi A, Mendola N, Nemeth B, Kalo Z. Multistakeholder Perceptions of Additional Value Elements for United States Value Assessment of Health Interventions. Value Health. 2024;27(1):15-25.
20. Syeed MS, Poudel N, Ngorsuraches S, Veettil SK, Chaiyakunapruk N. Characterizing attributes of innovation of technologies for healthcare: a systematic review. J Med Econ. 2022;25(1):1158-66.
21. Phelps CE, Lakdawalla DN, Basu A, Drummond MF, Towse A, Danzon PM. Approaches to Aggregation and Decision Making-A Health Economics Approach: An ISPOR Special Task Force Report [5]. Value Health. 2018;21(2):146-54.
22. Chalkidou K, Marten R, Cutler D, Culyer T, Smith R, Teerawattananon Y, et al. Health technology assessment in universal health coverage. Lancet. 2013;382(9910):e48-9.
23. Tsiachristas A, Cramm JM, Nieboer A, Rutten-van Molken M. Broader economic evaluation of disease management programs using multi-criteria decision analysis. Int J Technol Assess Health Care. 2013;29(3):301-8.
24. Howard S, Scott IA, Ju H, McQueen L, Scuffham PA. Multicriteria decision analysis (MCDA) for health technology assessment: the Queensland Health experience. Aust Health Rev. 2019;43(5):591-9.
25. National Institute for Health and Care Excellence (NICE). NICE health technology evaluations: the manual. Available at (https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation) Accessed August 2024.
26. Robinson MF, Mihalopoulos C, Merlin T, Roughead E. Characteristics of Managed Entry Agreements in Australia. Int J Technol Assess Health Care. 2018;34(1):46-55.
27. Institute for Clinical and Economic Review (I.C.E.R.). 2020-2023 Value Assessment Framework. 2020. Available at: (https://icer.org/our-approach/methods-process/value-assessment-framework/) Accessed August 2024
28. Accelerating Access to the best medicines for Australians now and into the future. Health Technology Assessment Policy and Methods Review – Final report. 2024. Available at:(https://www.health.gov.au/resources/publications/health-technology-assessment-policy-and-methods-review-final-report?language=en). Accessed January 2025
29. Institute for Clinical and Economic Review (ICER). Voretigene Neparvovec for Biallelic RPE65 mediated retinal disease. Available at: (http://www.icer-review.org) Accessed Ausgust 2024
30. National Institute for Health and Care Excellence (NICE). Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations [ID1054] Committee Papers. 2019 2019. Available from: (https://www.nice.org.uk/) Accessed Ausgust 2024
31. Merlin T, Laka M, Carter D, Gao Y, Choi YS, Parsons J, Milverton J, Ellery B, Newton S, Hill H, Morona J, Kessels S, Tamblyn D. Health Technology Assessment Policy and Methods Review: HTA Pathways and Processes, Clinical Evaluation Methods and Horizon Scanning. Canberra, ACT: Australian Department of Health and Aged Care, 2024. Available at: https://www.health.gov.au/resources/collections/health-technology-assessment-policy-and-methods-review-research-and-analysis-papers#final-hta-expert-papers.
32. Oliveira MD, Mataloto I, Kanavos P. Multi-criteria decision analysis for health technology assessment: addressing methodological challenges to improve the state of the art. Eur J Health Econ. 2019;20(6):891-918.
33. Kolasa K, Zah V, Kowalczyk M. How can multi criteria decision analysis support value assessment of pharmaceuticals? - Findings from a systematic literature review. Expert Rev Pharmacoecon Outcomes Res. 2018;18(4):379-91.

https://doi.org/10.1017/S0266462325100226 Published online by Cambridge University Press

481 *Table 1 Description of the broader elements of value and mechanisms to manage uncertainty in value assessment*
482 *presented in the survey*

Broader element of value
Labour Productivity: *Relates to costs associated with production loss and replacement costs due to illness, disability and death of productive persons, both paid and unpaid.*
Adherence: *Patient adherence and health outcomes relating to advantageous simpler dosing schedules, alternate routes of administration, or combination treatments over existing alternatives*
Reducing uncertainty due to a new diagnostic: *A companion diagnostic test that could differentiate "good responders" and "poor responders" may provide the ability to avoid an ineffective treatment in poor responders as well as costs and consequences of treatment-related adverse events*
Fear of contagion: *Reducing the anxiety associated with the risk of future illness, even if the expected number of cases prevented is low.*
Insurance value: *Reflects the value from an effective treatment for a disease reducing fear among all consumers of getting the disease.*
Severity of disease: *A gain in health may be more valuable to patients with a poor baseline prognosis (i.e., more severe disease).*
Value of hope: *Reflects the extent to which the chance for a cure is valued. For example, some patients may be willing to trade some survival (e.g. undertake a risky procedure) for a chance of a "cure" even if only for a small probability of cure/improved survival.*
Value to caregiver: *Extent to which health care can benefit family carers by reducing their caring responsibilities.*
Real option value: *Value generated when a health technology that extends life creates opportunities for the patient to benefit from other future advances in medicine.*
Scientific spillovers: *Broad societal benefit from knowledge created from a treatment with a new mechanism of action. It is considered a public good used for the discovery of other agents.*
Equity: *Fairness in the distribution of health and health care within society, across rich and poor, young and old, marginalized and not, employed or unemployed for example.*
Mechanisms to manage uncertainty in value assessment
Multiple Criteria Decision Analysis (MCDA): *A deliberative process where decision makers and stakeholders define the problem and determine the criteria, weighting and evidence requirements for a reimbursement decision.*
Willingness to pay (WTP): *Increase the ICER considered acceptable for treatments of rare diseases.*
Outcome based Managed Entry Agreements (MEA): *Allows earlier market access but requires CEA review once additional outcome data are available. For example: clinical data from pre- specified study protocol for all patients subsidised or from existing planned or progressing studies*
Financial risk share arrangements (RSA): *Financial subsidy based on medicine or patient performance. For example: Percentage rebate if the number of treatments per patient or accepted duration of treatment is exceeded. Subsidy ceases if patients do not meet agreed clinical measures*

483

484

https://doi.org/10.1017/S0266462325100226 Published online by Cambridge University Press

485 *Table 2 Background information for all stakeholders and by subgroup*

	Australian stakeholders (N=44)	*Australian stakeholder subgroups*	
		Academia (N=11)	*Private (consultants = 10, pharmaceutical industry=23)*
Years involved in HTA in Australia, mean	12.1 years	*7.3 years*	*14.3 years*
Position **Managerial, n/N (%)**	22/44 (50%)	*2/11 (18%)*	*20/33 (61%)*
Academic qualification, n/N (%)	14/44 (32%) Doctoral degree 27/44 (61%) Masters degree 3/44 (7%) Undergraduate degree	*8/11 (72%) Doctoral degree* *3/11 (27%) Masters degree*	*6/33 (18%) Doctoral degree* *24/33 (72%) Masters degree* *3/33 (10%) Undergraduate degree*
Area of academic qualification[a], n/N (%)	28/44 (64%) health economics 11/44 (25%) pharmacy 6/44 (14%) statistics 10/44 (23%) science 6/44 (14%) public health 7/44 (16%) business/economics/MBA	*9/11 (82%) health economics* *2/11 (18%) statistics* *1/11 (9%) science* *1/11 (9%) pharmacy* *1/11 (9%) public health*	*19/33 (58%) heath economics* *10/33 (30%) pharmacy* *9/33 (27%) science* *7/33 (21%) business/economics/MBA* *4/33 (12%) statistics* *1/33 (<1%) medicine* *5/33 (15%) public heath*

a. multiple disciplines reported per individual in some cases

487

488 *Table 3 Comparison between adequacy of HTA methods, sufficiency of public information and mechanisms for decision*
489 *making*

Q: Do you think the current HTA methods applied in Australia are adequate to appropriately assess the cost effectiveness of all medicines? n/N (%) agree		
Total cohort	5/43 (12%)	
Academia	*3/11 (27%)*	*RR: 4.36 (95%CI 0.84, 22.79) p=0.06*
Private sector	*2/32 (6%)*	
Q: Do you think the current HTA methods applied in Australia are adequate to appropriately assess the cost effectiveness of medicines for rare diseases? n/N (%) agree		
Total cohort	8/44 (18%)	
Academia	*2/11 (18%)*	*RR:1.0 (95%CI 0.24, 4.25) p=1.0*

https://doi.org/10.1017/S0266462325100226 Published online by Cambridge University Press

Private sector	*6/33 (18%)*		
Q: Do you agree that the current public information regarding reimbursement decisions in Australia provides sufficient information about which sources of value are considered and how they contributed to decision-making, n/N (%)			
Total cohort	11/41 (27%) agree	*Reasons for disagreement* 6/30 (20%) state we don't know which sources of value are considered 22/30 (73%) state while we know which sources of value are considered, we don't know how they contribute to decision-making 2/30 (6.7%) did not select a reason for disagreement	
Academia	*5/11(45%) agree*	*RR:2.27 (95%CI 0.87, 5.97) p=0.10*	*Reasons for disagreement* *-2/6 (33%) state we don't know which sources of value are considered* *-2/6 (33%) state while we know which sources of value are considered, we don't know how they contribute to decision-making* *-2/6 (33%) not sure*
Private sector	*6/30 (20%) agree*		*Reasons for disagreement* *- 4/24 (17%) state we don't know which sources of value are considered* *-20/24 (83%) state while we know which sources of value are considered, we don't know how they contribute to decision-making*
Q: Do you agree that an explicit checklist of sources of value beyond the patient QALY and whether they were considered by decision maker would be more informative than what is currently published in Australia? n/N (%) agree			
Total cohort	28/40 (70%)		
Academia	*5/10 (50%)*	*RR:0.65 (95%CI, 0.34, 1.25) p=0.11*	
Private sector	*23/30 (77%)*		
Q: Do you agree the following mechanism, MEA should be used in Australia in making decisions about reimbursement of medicines for rare disease, n/N (%) agree			
Total cohort	*32/40 (80%)*		
Academia	*9/10 (90%)*	*RR: 1.17 (95%CI 0.88, 1.56) p=0.36*	
Private sector	*23/30 (77%)*		
Q: Do you agree the following mechanism, RSA should be used in Australia in making decisions about reimbursement of medicines for rare disease, n/N (%)			
Total cohort	*33/40 (83%)*		

https://doi.org/10.1017/S0266462325100226 Published online by Cambridge University Press

Academia	*9/10 (90%)*	*RR: 1.13 (95%CI 0.86, 1.48) p= 0.47*
Private sector	*24/30 (80%)*	
Q: Do you agree the following mechanism, MCDA should be used in Australia in making decisions about reimbursement of medicines for rare disease, n/N (%)		
Total cohort	*29/40 (73%)*	
Academia	*7/10 (70%)*	*RR: 0.96 (95%CI 0.60, 1.51) p=0.84*
Private sector	*22/30 (73%)*	
Q: Do you agree the following mechanism, WTP should be used in Australia in making decisions about reimbursement of medicines for rare disease, n/N (%)		
Total cohort	*27/40 (68%)*	
Academia	*4/10 (40%)*	*RR: 0.52 (95%CI 0.24, 1.14) p=0.03*
Private sector	*23/30 (77%)*	

Abbreviations: CI, confidence interval; MEA, outcome based managed entry agreement (defined as allows earlier market access but requires CEA review once additional outcome data are available. For example: clinical data from pre-specified study protocol for all patients subsidised or from existing planned or progressing studies [26]); MCDA, multicriteria decision analysis (defined as involves a deliberative process where decision makers and stakeholders come together to define the problem and determine the criteria, weighting and evidence requirements for decision [24, 28]); RR, relative risk; RSA, financial risk share arrangement (defined as with subsidy based on medicine or patient performance. For example: Percentage rebate if the number of treatments per patient or accepted duration of treatment is exceeded. Subsidy ceases if patients do not meet agreed clinical measures [26]); WTP, willing ness to pay (defined as increase the ICER considered acceptable for treatments of rare diseases).

https://doi.org/10.1017/S0266462325100226 Published online by Cambridge University Press

Table 4 Comparison between sources of value that should be considered in HTA for all medicines and medicines for rare disease

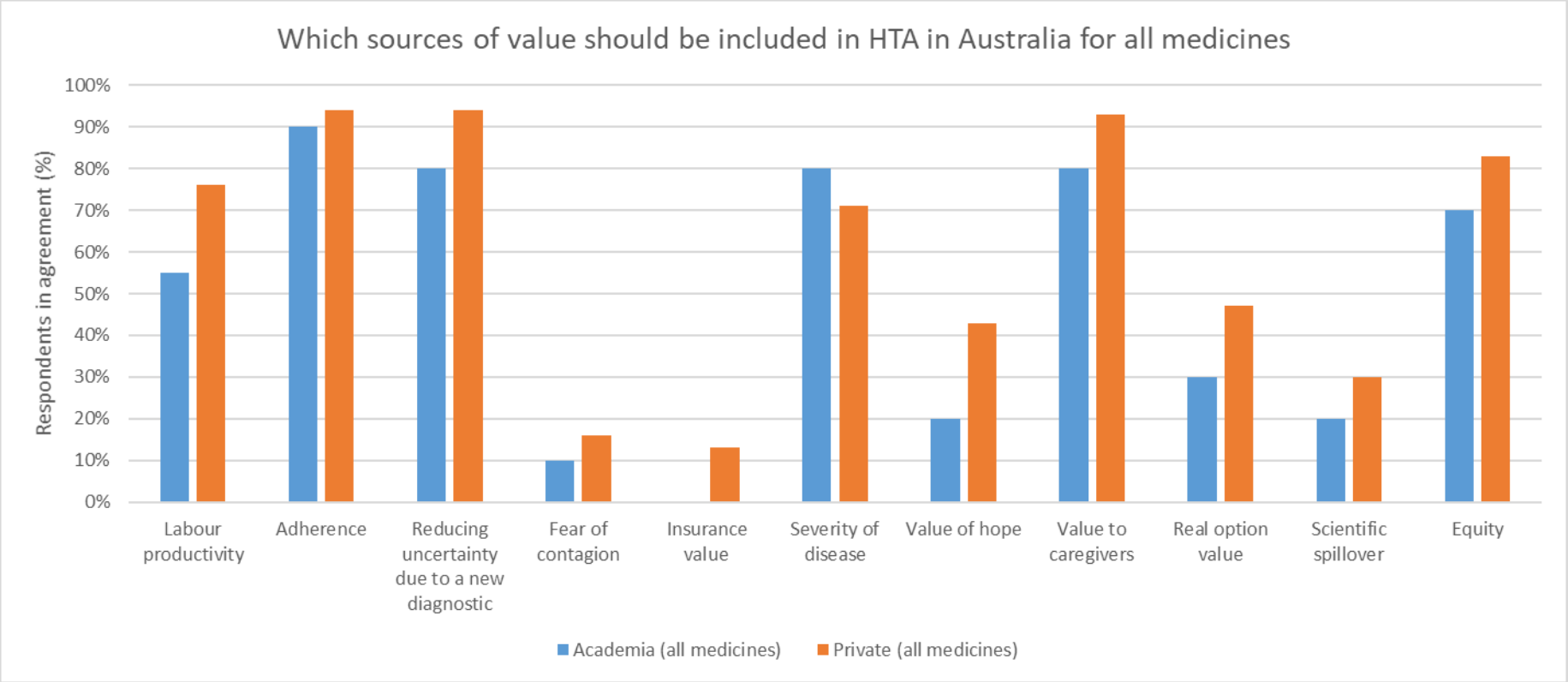
Broad elements of value	All medicines, n/N (%) agree				Medicines for rare disease, n/N (%) agree			
	Total cohort	*Stakeholder sectors*			Total cohort	*Stakeholder sectors*		
		Academia	*Private sector*	*RR (95%CI), p-value*		*Academia*	*Private sector*	*RR (95%CI), p-value*
Labour productivity	31/43 (72%)	*6/11 (55%)*	*25/32 (78%)*	*0.70 (0.40, 1.23), 0.1326*	26/40 (65%)	*5/10 (50%)*	*21/30 (70%)*	*0.71 (0.37, 1.39), 0.2508*
Adherence	39/42 (93%)	*9/10 (90%)*	*30/32 (94%)*	*0.96 (0.77, 1.20), 0.6877*	34/40 (85%)	*8/10 (80%)*	*26/30 (87%)*	*0.92 (0.66, 1.30), 0.6091*
Reducing uncertainty due to a new diagnostic	37/41 (90%)	*8/10 (80%)*	*29/31 (94%)*	*0.86 (0.62, 1.18), 0.2093*	34/40 (85%)	*7/10 (70%)*	*27/30 (90%)*	*0.78 (0.51, 1.19), 0.1250*
Fear of contagion	6/41 (15%)	*1/10 (10%)*	*5/31 (16%)*	*0.62 (0.08, 4.70), 0.6335*	4/40 (10%)	*1/10 (10%)*	*3/30 (10%)*	*1.0 (0.12,8.56), 1.00*
Insurance value	4/41 (10%)	*0*	*4/31 (13%)*	*ND*	6/40 (15%)	*1/10 (10%)*	*5/30 (17%)*	*0.60 (0.08, 4.54), 0.6091*
Severity of disease	30/41 (73%)	*8/10 (80%)*	*22/31 (71%)*	*1.13 (0.77, 1.65), 0.5751*	31/40 (78%)	*8/10 (80%)*	*23/30 (77%)*	*1.04 (0.73, 1.51), 0.8270*
Value of Hope	15/40 (38%)	*2/10 (20%)*	*13/30 (43%)*	*0.46 (0.13, 1.70), 0.1869*	9/40 (22%)	*1/10 (10%)*	*8/30 (27%)*	*0.38 (0.05, 2.64), 0.2744*
Value to caregivers	36/40 (90%)	*8/10 (80%)*	*28/30 (93%)*	*0.86 (0.62, 1.19), 0.2235*	35/40 (88%)	*7/10 (70%)*	*28/30 (93%)*	*0.75 (0.50, 1.14), 0.0533*
Real option value	17/40 (43%)	*3/10 (30%)*	*14/30 (47%)*	*0.64 (0.23, 1.78), 0.3558*	11/40 (28%)	*0*	*11/30 (37%)*	*ND*
Scientific spillover	11/40 (28%)	*2/10 (20%)*	*9/30 (30%)*	*0.67 (0.17, 2.58), 0.5397*	10/40 (25%)	*1/10 (10%)*	*9/30 (30%)*	*0.33 (0.05, 2.32), 0.2059*
Equity	32/40 (80%)	*7/10 (70%)*	*25/30 (83%)*	*0.84 (0.54, 1.30), 0.3613*	34/40 (85%)	*8/10 (80%)*	*26/30 (87%)*	*0.92 (0.66, 1.30), 0.6091*

Abbreviations: CI, confidence interval; ND, not determined; RR, relative risk

Note: The questions posed to participants were, "Rate the extent to which you agree or disagree that the following source of value should be considered in HTA of medicines in Australia", and then participants nominated if they were aware of methods to include each source of value in a cost effectiveness analysis (presented in Table 5); a table of 11 value elements was then presented to participants and they were asked "Do you agree that the following sources of value should be considered in cost effectiveness analysis of a medicine for rare disease in Australia?" for each value.

https://doi.org/10.1017/S0266462325100226 Published online by Cambridge University Press

508 *Table 5 Comparison between stakeholder groups regarding sources of value that should be considered in HTA for all medicines and suggested methods to include them into EE's*



Suggested methods related to assessment of costs or outcomes:

Productivity: human capital approach, friction cost, willingness to pay study, patient preference, G	**Adherence:** persistence, discontinuations, observed utilization within trial and post	**Reducing uncertainty**: decision tree/ Bayes revision node to capture test accuracy before modelling costs & outcomes in responders	**Severity:** utility study, ICER threshold, QALY weighting, scenario analysis (using results from complementary subgroups), specific	**Value of hope**: Utility studies (Time trade off, standard gamble and other preference based measures).	**Value to caregivers**: Productivity, indirect carer costs, CareQoL and other measures of utility	**Equity:** Threshold increase, equity weightings, funding for specific populations, subgroup analysis, distributional cost-

https://doi.org/10.1017/S0266462325100226 Published online by Cambridge University Press

method[27]	listing surveillance	and non-responders,	funding pools			effectiveness analysis

509

510

https://doi.org/10.1017/S0266462325100226 Published online by Cambridge University Press