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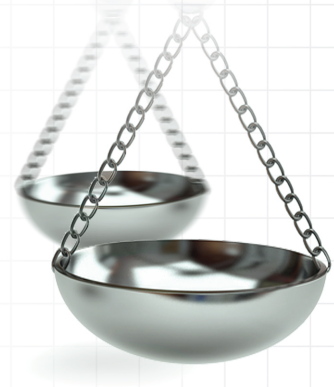

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Val (EU) xit: do we need an international ISPOR value flower?

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"This paper reflects on the elements of value which were defined in the ISPOR value flower and critiques their relevance in the context of jurisdictions in Europe, Australia and Canada from the perspective of both patients and (largely) single payers who have decisions informed by HTA."

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Background

In 2016, an International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Special Task Force (STF) was formed to evaluate a number of frameworks to value pharmaceuticals that were being developed within the US by several different stakeholders, including from the second panel on cost–effectiveness in health and medicine, from a health economics perspective [1,2]. To carry out its mission, the STF assembled a core group of experts in health economics, including, non-US experts. The health economics perspective adopted by the STF led to an emphasis on considering patients as both purchasers of health insurance and recipients of healthcare services. This perspective also had implications for the STF's conceptualization of the value of pharmaceuticals [3].

In terms of defining elements of value for a medicine, the STF acknowledged the merits of the traditional cost per quality-adjusted life-year (QALY) approach as a foundation for discussions concerning value assessment. However, it also recognized the limitations inherent in this metric [4]. The STF identified and considered 12 potential elements of value, including two core elements of QALYs and net costs, two common but inconsistently used elements (productivity and adherence improvement) and eight potentially 'novel' elements (reduction in uncertainty, fear of contagion, insurance value, severity of disease, value of hope, real option value, equity and scientific spillovers). The 'ISPOR value flower', a figure found in the 2018 report of the ISPOR STF, visually highlights all these aspects of value. Modified versions of the value flower have since replaced adherence improvement with family spillover (Figure 1). The idea of the flower was to help broaden the view of value in healthcare and spur new research on incorporating additional elements of value in traditional cost–effectiveness analysis (CEA).

The report has been cited over 400-times since it was published. Although it has received significant attention, no major US public or private insurer has adopted it explicitly as a comprehensive evaluation framework, and therefore it is an open question as to how practically useful it has been. The impact of the report on how health technology assessment (HTA) agencies globally appraise medicines has also been limited to date. Breslau and colleagues reviewed 53 HTA guidelines representing 52 countries and collected data on whether each guideline mentioned elements of value [5]. Breslau *et al.* evaluated 21 value elements in total; looking at the ten elements of value from the original ISPOR value flower (all elements apart from QALYs and net costs and considering adherence instead of family spillover); HTA guidelines on average mentioned only three out of ten of these elements. Importantly, mention of value elements in guidelines does not necessarily mean that HTA bodies use these elements in their ultimate decision making; indeed, these elements were rarely suggested to be included in base-case analyses.

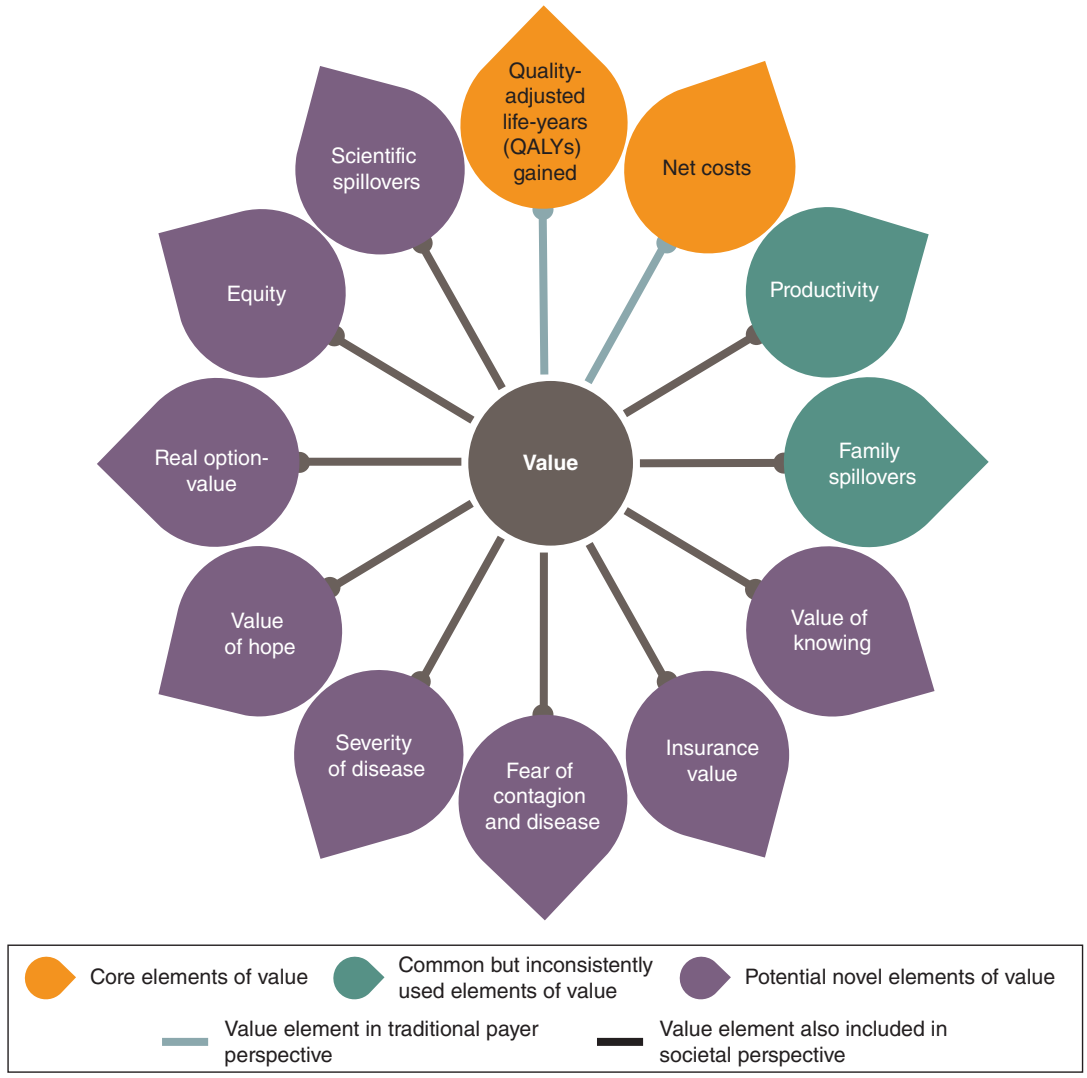

Figure 1. The International Society for Pharmacoeconomics and Outcomes Research value flower.
Adapted from Lakdawalla *et al.* [4].

The motivation for the emerging value frameworks in the US were related to concerns about the rising price of new medicines, and the STF focused on the issue of value as an incentive for innovation. HTA considerations are broader, being pertinent for a series of related health system decisions for medicines (e.g., incorporation into guidelines). In thinking about how the ISPOR value flower might be useful in countries outside of the US, it is perhaps useful to compare two alternatives: a non-US archetype with the pluralistic (or fragmented) US insurance system. Arguably, the major distinction is that non-US systems provide universal health coverage (UHC): all citizens are in the same health plan and lifetime risk-sharing pool. Although there is usually private sector supplemental insurance available, for the large majority of health spending, the government is a single-payer operating with an annual budget. This archetype most represents jurisdictions in Europe, as well as Australia and Canada, where mature HTA processes exist to evaluate health technologies for single-payers. Therefore, it is possible that HTA agencies are not considering some elements of value from the flower because they are not as applicable to a non-US archetype. This paper reflects on the elements of value which were defined in the ISPOR value flower and critiques their relevance in the context of jurisdictions in Europe, Australia and Canada from the perspective of both patients and (largely) single payers who have decisions informed by HTA. In doing so, we hope to further the routine consideration of elements of value by HTA agencies and drive research into the best approaches to incorporate them into HTA.

Assessment of value element relevance to Europe, Australia & Canada

Table 1 shows our assessment of whether each of the ISPOR value elements are relevant from a single-payer or non-US patient perspective from a targeted literature review. We also noted whether European, Canadian or Australian HTA guidelines consider these value elements using data from Breslau *et al.*, with the acknowledgement that inclusion in guidelines does not mean they are actually used in decision making. An additional caveat is that while the non-US archetype may reflect a 'single-payer', currently payers generally only consider impact on healthcare budgets, whereas we have considered an ideal situation where a government budget is considered holistically. The only elements currently not mentioned in any European, Australian or Canadian HTA guideline is insurance value and the fear of contagion. Given their lack of inclusion in any HTA guideline, we discuss next the potential reasons for this.

Insurance value-lost in translation?

Perhaps the primary reason for the lack of inclusion of 'insurance value' in European, Australian or Canadian HTA guidelines reflects the differing healthcare systems between these countries and the USA. The ISPOR STF described the element of insurance value as having two separate contributing elements. The first element is that of physical risk, in other words, the risk of a healthy individual becoming sick. With the availability of a novel intervention for a particular disease or condition, the risk for a healthy person getting sick is reduced and/or the 'sick' state is less unpleasant. This element of insurance value is undoubtedly important to people regardless of the nature of the healthcare system in their country, and perhaps best exemplified by COVID-19 vaccines reducing the risk of getting sick or experiencing severe complications [6,7]. Vaccines meant that we all had less to fear from it, even though not all of us would develop COVID-19. The second element of insurance value is financial risk protection which considers the importance of medical insurance covering novel interventions to protect healthy individuals from paying for the medical costs that the new intervention would avert. The financial risk protection aspect of insurance value is, however, not as relevant for single-payer/universal healthcare countries where there is little financial risk to a patient for the costs of medical care (although private insurance does exist in these countries for those who want to access services faster). As such, it is notable how for countries outside of the USA, the concept of insurance value has been used differently. For example, the UK Office for Health Economics has used insurance value in the context of assessing the value of novel antibiotics [8]. In this setting, it is seen as the value associated with avoiding potential costs to health systems and society through making a treatment such as a novel antimicrobial available, or keeping it in reserve, for a range of adverse scenarios where anti-microbial resistance could become substantially worse. The potential insurance value of a novel antimicrobial for the UK, under the assumption that antimicrobial resistance levels remain at the levels seen today, was calculated to be £718 million over a decade, reflecting the increase in operational healthcare costs needed, as well as the broader societal impact involving population disease transmission, productivity loss and informal care [9]. Therefore, while physical risk protection should be appraised from a patient perspective in Europe, Australia and Canada, for a more relevant value flower, financial risk protection could be seen from the perspective of the payer, specifically as the societal costs of not having a treatment in place (for example, the costs of additional nursing homes for patients with dementia). In summary, while there is currently no common definition of insurance value, it appears to be relevant in all countries regardless of payer archetype.

No fear of (European) contagion?

The ISPOR STF described the 'fear of contagion' as the anxiety associated with the risk of a future spread of an infectious disease, such as Ebola, and the value an intervention can bring in reducing this anxiety. Despite not being explicitly mentioned in European HTA guidelines, it has nevertheless been evaluated in non-US HTA. Yuasa *et al.* investigated appraisals of hepatitis C drugs and found that the Australian HTA agency, the Pharmaceutical Benefits Advisory Committee (PBAC) and the English HTA body, the National Institute for Health and Care Excellence (NICE) both recognized how hepatitis C treatments can reduce transmission and therefore fear of disease spread [10]. Perhaps the reason why it is not explicitly mentioned in HTA guidelines is due to the limited instances of epidemics broadly afflicting European countries (and Western European mature HTA agency guidelines influence HTA guidelines across the globe) and relatedly, vaccines only represent a small fraction of technologies assessed by HTA bodies. However, as we emerge from the COVID-19 pandemic, perhaps this will change in preparation for future infectious disease outbreaks. Empirical estimates for the fear of contagion in Europe, Australia and Canada are also lacking – a general problem for many value elements which we will discuss next.

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Table 1. The relevance of the International Society for Pharmacoeconomics and Outcomes Research value flower elements from a patient and single-payer perspective in Europe, Australia and Canada and their inclusion in European, Australian or Canadian HTA guidelines.

Value element	Relevant in Europe, Australia and Canada-single-payer perspective?	Relevant in Europe, Australia and Canada-patient perspective?	Countries currently mentioning in HTA guidelines (data from Breslau *et al.*)	Ref.
Reduction in uncertainty	Yes – relevant in terms of more efficient use of technologies	Yes – knowledge of who would benefit would be valued	Australia, Canada, Denmark	[23,24]
Fear of contagion	Not applicable	Yes – people would value a technology that reduces their fear that they may catch an infectious disease	None	[25]
Insurance value	Potentially. In the case of anti-microbials it has been classified as the societal value of having a treatment available in case of a future major or rapidly escalating health problem	Yes- physical risk protection is relevant as healthy individuals would value knowing there is a treatment available for them should they fall sick, however this has not been well quantified empirically. No for financial risk- with universal healthcare coverage this is less relevant	None	[6,9]
Severity of disease	Not applicable	Yes – evidence exists that society places additional value on treatments for those with severe disease	Australia, Belgium, Canada, Czech Republic, France, Germany, Ireland, Norway, Scotland, Slovenia, Switzerland	[26]
Value of hope	Not applicable	Yes – potentially relevant, however the risk appetite for EU patients has not been well quantified	Denmark	[27]
Real option-value	Not applicable	Yes – patients would value an extension of life to benefit from future medical innovations	Denmark	[28]
Equity	Yes – society is willing to trade efficiency against inequality	Yes – society is willing to trade efficiency against inequality	Australia, Belgium, Canada, Croatia, Czech Republic, England, France, Germany, Hungary, Ireland, Norway, Poland, Slovenia, Spain, Switzerland	[29]
Scientific spillovers	Yes – pharmaceutical innovation should enable other organizations to generate new value for payers in the future	Yes – the potential of knowledge spillovers leading to better drugs in the future would be valued	England, Scotland	[30,31]
Family spillover	Yes – relevant in terms of humanistic and economic cost of diseases impacting caregivers	Yes – relevant in terms of humanistic impact on caregivers	Baltics, Belgium, Croatia, Czech Republic, Denmark, England, Finland, France, Germany, Ireland, Italy, The Netherlands, Norway, Poland, Portugal, Scotland, Spain, Sweden, Switzerland	[32,33]
Adherence improving factors	Yes – relevant in terms of more efficient use of technologies	Yes – relevant as it should increase a technology's benefit	Australia, Canada, Germany, Hungary, Ireland, The Netherlands, Norway, Scotland, Slovakia, Slovenia, Spain	[34,35]
Productivity	Yes – relevant in terms of tax revenues	Yes – relevant given financial and quality of life benefits	Austria, Australia, Belgium, Canada, Czech Republic, Denmark, England, Finland, France, Germany, Hungary, Ireland, Italy, The Netherlands, Norway, Poland, Spain, Sweden	[36,37]

Relevance was assessed using data from a targeted literature review.

Where's the non-US data?

The value elements 'value of hope', 'real option value', 'reduction in uncertainty' and 'scientific spillovers' have had limited uptake in European, Australian or Canadian HTA guidelines being seen in guidelines for one to three countries. It is likely that the limited consideration of these value elements is because the inherent value assigned to these elements by patients or society has not been quantified well in Europe, Australia or Canada. For example, the value of hope describes the value that a patient may place on the chance (however small) that a treatment which offers a wider range of potential outcomes, gives them a significant benefit. This is well demonstrated in oncology, where advanced cancer patients in the USA value the hope of a large survival gain from a treatment, independent of the therapy's average mortality improvement [11]. No study has yet been conducted to investigate this preference from a non-US patient perspective [12,13]. The same is also true for real option value and reduction in uncertainty. The concept of real option value suggests that value may be generated when a medical technology extends life for a patient long enough so that they may potentially benefit from the next treatment innovation. An example using US real-world data showed that for patients with advanced or metastatic melanoma, 50% receiving first-line ipilimumab survived long enough to receive a more efficacious immunotherapy (pembrolizumab) after its FDA approval as compared with only 18% who received first-line chemotherapy [14]. Similar studies could easily be performed using non-US real-world data but have not been done to date. For reduction in uncertainty there is also the fact that diagnostics generally have different HTA processes than those used for medicines [15], so it is plausible that the ISPOR value flower has been slower to permeate into the area of diagnostics assessment as compared with medicines. Scientific spillovers, referring to positive knowledge externalities arising from the development of a product, has received little attention globally in terms of attempts to quantify. Delandistrogene moxeparvovec, a newly approved gene therapy for Duchenne muscular dystrophy, can serve as an example of scientific spillovers. Learnings from the development of this therapy around adeno-associated virus gene delivery are already being used to inform development of other gene-based treatments in areas ranging from efficiency of viral vectors and ability to scale manufacturing volumes [16]. There is limited research in this area perhaps due to the difficulties in robustly enumerating the positive externalities arising from innovation. There may also be reluctance from agencies to factor in elements like scientific spillovers and option value, as they depend on as yet undiscovered innovations. There is also the issue that HTA agencies have a narrow remit and do not consider spillovers outside of healthcare. To conclude, a number of value elements have limited quantification in non-US settings, and attempts need to be made to quantify these elements for HTA decision makers to deliberate upon.

What methods to use?

There are two general challenges when it comes to novel value elements and HTA. First, how to measure these elements and second, once measured how to incorporate them into decision making. For elements such as severity of disease, equity, family spillovers, adherence improving factors and productivity, while they have been included in many HTA guidelines, there is not clear methodological guidance as to how to best incorporate these factors into CEA, and importantly also whether or not CEA is the most optimal way to incorporate such evidence, and as such they are not routinely considered in HTA decision making. For example, for family spillovers there are questions around how to incorporate caregiver quality of life into health economic models due to the lack of consensus on aggregating QALYs across multiple individuals [17]. For equity, while there is increasing awareness of health equity across HTA bodies, it is not yet routinely considered by them. Potential approaches to do so range from quantifying inequalities in the unmet need of the label patient population through to more specific assessments such as distributional cost–effectiveness analyses which can help to provide information about the equity impacts of new health technologies as well as trade-offs that might arise between equity and efficiency [18]. This method however requires further demonstration studies including country-specific considerations such as domains of equity of most relevance to enable adoption routinely by HTA agencies. There still remains the challenge of how to translate results into greater rewards for innovation. In Europe, not all countries have a distinct role for CEA in decision making, for example Germany. For these non-cost–effectiveness HTA systems, there is a need to understand how these value elements could be considered in decision making, including transparency in how these elements are weighted and prioritized.

Do we need more petals?

The US second panel on cost–effectiveness in health and medicine took a public health perspective when determining what additional aspects of value to include in societal CEA [2]. These aspects included social services, education,

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criminal justice, housing and the environment. Given the governmental single-payers in Europe, Australia and Canada for healthcare are also responsible for all these other societal costs or issues, it is perhaps sensible to consider these in an international value flower to foster decision making based on total costs to governments rather than a siloed healthcare-only perspective.

These elements again all need quantification but there are some data already to support their inclusion. For example, a study in Denmark has shown that parental cancer can negatively impact children's educational outcomes, especially if the cancer is one that has a poor prognosis (e.g., limited treatment options) [19] and an investigation in Sweden demonstrated that treatment for mental health disorders significantly reduces the rate of crime [20].

Moreover, healthcare is responsible for up to 8% of a country's carbon dioxide equivalent emissions annually [21]. The emissions are primarily derived from the healthcare supply chain through the production, transport and disposal of goods and services, such as pharmaceuticals, medical devices, hospital equipment and instruments. By incorporating environmental impact in decision-making, HTA has the potential to influence the impact of carbon footprint of new technologies. Crucially, this will not only impact current global health outcomes, but those of future generations [22].

Conclusion

The limited adoption of the ISPOR value flower by HTA agencies in Europe, Australia and Canada may be attributed to various factors. The relatively recent release of the STF report may contribute to the current lack of widespread use. Additionally, there are undoubted challenges associated with altering established HTA agency practices, and the lack of compelling incentives for HTA agencies to incorporate non-health effects into their recommendations for spending healthcare budgets. In UHC settings, legislation underpins value assessments and therefore this likely will need a wider consultation.

We contend that the ISPOR value elements should matter both in UHC systems outside the USA and in the USA. However, their impact will vary depending on the degree of risk aversion and baseline severity of the population as well as health system productivity and costs. Our call for action is to ensure that the single-payer and non-US patient perspective is considered. This may influence how some value elements are quantified (e.g., insurance value), and also lead to the inclusion of additional petals. We need more collaborative research that engages HTA bodies to generate European, Canadian and Australian value element estimates as well as to decide upon the best modelling approach to drive enhanced inclusion of these estimates into CEA. For example, by definition, a health system with UHC places a higher weight on equity than one without UHC. Methodology to transparently use value elements for decision making in HTA systems not using CEA must also be established. This is perhaps all the more important as we move to a EU HTA and a separate value flower tailored specifically to Europe, Australia and Canada may help to stimulate all of this.

To conclude, we argue that the ISPOR value flower has been useful both in the USA and outside the USA in stimulating discussion and research about the broader impact of new medicines on societal well-being. The standard cost–effectiveness framework of health economics has been and remains a useful starting point. But if we begin to recognize and address some of its limitations, we should be able to better steer innovation in the direction of global dynamic efficiency, thereby also providing an opportunity to improve global health equity as well.

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Competing interests disclosure

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Writing disclosure

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