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EDITORIAL

Are current ICER thresholds outdated? Valuing medicines in the era of personalized healthcare

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According to the Orphanet database, there are, at present, 495 drugs that have been granted orphan or ultra-orphan designation (i.e. affecting no more than 5 in 10,000 and 1 in 50,000 people, respectively [1]). Within the European Union (EU), 88 drugs have received market authorization from the European Medicines Agency (EMA), of which nearly one-third was granted in 2014 and 2015. Given that orphan drugs as well as cytotoxic chemotherapy – or cancer drugs – have been driving the number of new molecular entities approved by the EMA, and its counterpart in the USA, and cost many patients health systems dearly, the issue of access in the age of personalized healthcare is increasingly and inextricably linked to affordability and willingness to pay for better outcomes [2,3]. Indeed, in the absence of EU legislation to guide the prices and use of orphan and cancer drugs among member states, there are considerable differences in patient access to medicines that make the routine application of health technology assessment (HTA) more challenging [2].

Since the market for orphan drugs is small and their prices are associated with high monetary cost, these drugs rarely meet conventional reimbursement criteria, be they formal cost-effectiveness requirements or other therapeutic added value relative to cost hurdles [4]. This also holds for cancer drugs. A recent study which compared the cost-effectiveness of cancer versus noncancer drugs, for example, found that the mean and median of incremental cost-effectiveness ratio (ICER) calculated for an intervention using the former were $138,582/quality-adjusted life-year (QALY) and $55,500/QALY, respectively, compared with $49,913/QALY and $31,000/QALY, respectively, for an intervention with noncancer drugs [5]. Among cancer drugs, 45% had ICERs below $50,000/QALY and 70% below $100,000/QALY. Meanwhile, threshold ICERs based on reimbursement and coverage decisions range from £20,000/QALY in England to €80,000/QALY in the Netherlands [1,6]. While the simplicity and ease of application of the ICER threshold (to just about any drugs and health technologies) make it very appealing, one cannot escape the deficiencies of the QALY as an outcome measure, and the arbitrariness (of the derivation) of the threshold as illustrated in the case of $50,000/QALY in the USA [7].

Fortunately, orphan, ultra-orphan, and cancer drugs are often reimbursed. In the Netherlands, for example, no drugs have been withheld because of their unfavorable cost-effectiveness, as in the case of nivolumab in the treatment of non-small cell lung cancer. Moreover, a special program is in place to support hospitals financially in prescribing expensive orphan drugs. Meanwhile, England has promoted to facilitate patient access to cancer drugs not (routinely) available in the National Health Service through the Cancer Drugs Fund [8]. Although the policy on reimbursement of cancer and/or orphan drugs is recently revised to better capture value for money, there are essentially two thresholds in the UK, given distinct and separate budgets and differential weights on health outcomes. In both the Netherlands and England, negotiations with pharmaceutical manufacturers on effective/actual prices have been instrumental in facilitating reimbursement of and patient access to drugs.

In the era of personalized healthcare, the evidence base for a new drug's efficacy and safety is likely to be smaller, giving a relatively imprecise ICER. Indeed, a systematic review of orphan drugs in oncology found that drugs marketed in the USA have varying levels and quality of clinical evidence and a paucity of evidence regarding economic value [9]. As personalized healthcare advances, there will be more drugs developed targeting a molecular defect or single mutation found in small(er) subsets of patients to prolong survival as well as better quality of life (QoL), but may also generate smaller population benefits [7]. Were the size of the health budget and our collective willingness to pay to remain the same, are we ready to deal with the intended and unintended consequences of investment and disinvestment? Han et al. [10] found, for example, that Canadian physicians have resorted to, among other methods, falsifying claims on access forms to obtain unfunded oral chemotherapies for their patients.

With new treatments developed for limited patient populations whose health outcomes may or may not be deemed commensurate to the high(er) price tags of medicines, and given that the majority of EU member states surveyed on their respective orphan drug regulations and policies have cost-effectiveness as an HTA requirement [3], we need to deal

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with the uncomfortable quandary of allocating scarce healthcare resources while meeting the needs of patients whose conditions, although individually are rare, collectively affect tens of millions. This is made more pronounce by studies that show decisions on funding policies, which are supposed to reflect societal values, often differing [11], and that different stakeholders have different priorities and preferences [12].

To illustrate, oncologists and healthcare policy makers reward survival gain more than an improvement in QoL, whereas patients and the general population show a preference for QoL improvements related to cancer treatment survival benefits [6]. It has been shown that among medical professionals, family physicians value life-prolonging and QoL-enhancing interventions roughly equally, while oncologists value interventions that extend survival more highly than those that improve only QoL [13]. Oncologists required an average of six additional months of life for a cancer drug that costs $75,000, which implied an ICER of $100,000/QALY, and 7–8 months for a drug that costs $150,000, suggesting an ICER of $192,308/QALY [14]. Although these findings may not be generalizable across different healthcare systems, willingness to pay varies between stakeholders and across societies and invokes wider concerns than maximization of QALYs [11,12].

Whereas the acceptance of higher costs per QALY and lack of consensus on the ICER threshold can be viewed from different perspectives, it is a sign of the limited and waning legitimacy of current HTA approaches that lead decision-makers to question, if not, dismiss cost-effectiveness analyses and revert to political or organizational interests [15]. While the traditional health economist view does not consider other factors and that valuations are restricted to health outcomes [4], members of society do give weight to other factors than just survival and QoL and have different priorities, as can be inferred from above [13,14]. A wider perspective and evaluation and enhanced assessment space are needed to capture other components of value and account for (differences in health) budget (also over time), local costs and prices, disease burden, and societal values [7,15].

Where the goal is maximizing utility and rewarding medicines for the value they create, the use of conjoint analysis methods and multicriteria decision analysis (MCDA) serves as a means of providing an enhanced framework for assessing value [12]. By using a structured, explicit approach to decision-making involving multiple criteria, MCDA can help increase the consistency, transparency, and legitimacy of decisions [16,17]. In identifying, collecting, and structuring the information required by those making judgments, including, but not limited to, payers and health authorities, it supports the deliberative process which has been argued to be weak in the conduct of HTA. With MCDA, elements of value can be measured and scored in their natural units or through constructed scales, qualitatively or quantitatively, and weights are assigned to reflect criteria importance when combining them [17]. If multiple criteria are relevant for the assessment of the value of an orphan drug to an HTA, then explicitly or implicitly MCDA is applied.

The EMA has explored the use of MCDA for regulatory decision-making when different features of benefit and risk have to be prioritized [18]. Meanwhile, the American Society of Clinical Oncology and the European Society for Medical Oncology have developed their respective value scales to assess new cancer therapies and to summarize the relevant evidence, which are both partial forms of MCDA. Although the statistical and methodological rigor of both scales is subject to debate, they are intended to serve as tools for evaluating the benefits of a new therapy, and to serve the purpose of facilitating patient-doctor conversation on the use of specialty drugs in the context of targeted treatment [19,20]. There are many MCDA methods available, which differ in terms of use, as well as the fundamental theories and beliefs underpinning them. However, it may be best that different stakeholders support the use of a few frameworks and methods since multiplicity and complexity may only complicate the assessment of therapeutic drugs and biologics and their companion diagnostics.

The value of orphan and cancer drugs is multidimensional. Many important factors affecting value are not adequately reflected in the current HTA process. Where drugs are strategically priced at the ICER threshold and, thus, reimbursed, such may not lead to an increase in the population's health. Where survival or QALYs gained is regarded as the outcome of interest, we may fail to capture the full value of a drug, thereby undermining the well-being of patients who have uncommon treatment needs and research and development investments, which are publicly underwritten using push and pull incentives. MCDA may assist in guiding the proper valuation of drugs in the era of personalized healthcare by providing nuanced, context-specific information that decision-makers require. In addition to using MCDA methods amidst global cost-effectiveness thresholds, we need to continue discussion of what health systems are willing to pay for innovation at present and in the not so distant future.

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