A proposal for value informed, affordable (“via”) prices for innovative medicines

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**Introduction**

Truly innovative medicines can reduce both mortality and morbidity, thereby increasing the length and/or the quality-of-life of patients. However, many of these medicines come at an extra cost compared to the standard of care, and that extra cost is sometimes substantial. At the OECD Ministerial Meeting on “Next Generation of Health Reforms” (January 2017), Ministers underlined that new generation treatments are indeed very costly, with significant budget impact implications. Several authors have expressed these concerns as well, especially pointing to – but not restricting to – orphan medicines and cancer drugs. Others point moreover to the evidentiary uncertainty for some of these treatments, which compromises the justification of the high prices.

The Expert Panel on Effective ways of investing in Health recently stated that there is a need for innovative payment models to ensure that innovation “that matters” is produced, that patients have access to innovation, and that healthcare systems are financially sustainable.

For many years, cost-effectiveness has been applied as a key criterion to assess whether new medicines and other technologies deserve to be reimbursed within healthcare systems, but there is debate on what actually can be considered as cost-effective, which elements must thereby be considered, and how these can guide the pricing and reimbursement of medicines concretely.

The current conceptual paper proposes an innovative payment model that implies the explicit use of cost-effectiveness, medical need, and budget impact for the assessment and appraisal of the price and reimbursement level of innovative medicines.

**Cost plus versus value based pricing**

One of the current observations, according to a recent report by the World Health Organization, is that the prices of innovative medicines bear little or no relationship with R&D costs. It has, therefore, been argued that prices should better reflect investments for Research and Development (R&D), a logic which is sometimes referred to as “cost plus pricing”.

The argument is that the starting point for price negotiations should be an agreement among all parties about how much it costs to develop a new medicine. Although this approach might at first sight seem fair and logic, it raises several issues:

- First, it may lead to the wrong incentives, in that the higher the R&D costs, the higher the price that theoretically could be justified.
- Second, investment costs for medicines that eventually do not make it to the final stage (i.e., access to patients), because of insufficient effect or due to toxicity, or other reasons, must be amortized and factored into the cost of R&D of the medicines that make it to the market, which may then lead to a perverse situation where a company with many of such failures could justify a higher price for the few products that make it to the market.
- Finally, this approach does not sufficiently encourage true innovation. Irrespective of the benefit to patients, reward will be according to R&D costs. Hence, cost plus pricing does not reward value.

A recent cost plus price proposal from Uyl-De Groot and Löwenberg tried to address the last issue, but in a rather arbitrary way, and not solving the first two issues.

It seems that a better approach is to start from the principle that decisions on pricing and reimbursement for innovative medicines should account for the added value they deliver for patients and society, i.e., the so-called “value based pricing” approach. This requires first of all a better insight in the meaning of value. Recently, the ISPOR Special Task Force on US Value Assessment Frameworks provided a broad overview of the different possible interpretations of value. Neumann et al. point to the widespread use of QALYs (quality adjusted life years) as a core element of value, but also observe that this metric has limitations: “QALYs may not always fully capture the health (or well-being) of patients, or incorporate individual or community preferences about the weight to be given to health gain, for example, about disease severity, equity of access, or unmet need”. Hence, better outcomes should not be the sole criterion. For instance, from the original work of Erik Nord, it
appears that societal willingness to pay for new treatments depends strongly on the degree of severity or suffering associated with the current situation. This has also been confirmed in more recent work, such as in Shiroiwa et al.\textsuperscript{18} and Richardson et al.\textsuperscript{19}, where the latter suggest that higher willingness to pay is especially relevant for very severe conditions. Value should, therefore, be defined at least by both disease and treatment related characteristics, which should both be objectivized.\textsuperscript{20,21}

The principle of value based pricing is then based on the general economic concept that prices of new goods indicate the difference between what currently available goods offer and the value that the new goods can provide\textsuperscript{22}. According to this logic, the higher the added value (in its broader interpretation), the higher the price the innovation deserves. This, however, entails two important questions: (1) How much should society be willing to pay for additional value? And (2) What to do if the added value is subject to evidentiary uncertainty?

**Value for money: issues with the threshold**

Value does not necessarily mean “value for money”. Price and reimbursement levels of medicines should reflect an acceptable value for money from a (public) payer’s perspective. This means that, in the interpretation of cost-effectiveness results, it is important to apply thresholds: the maximum amount of money a payer or a society is willing to pay for gaining QALYs needs to be made explicit. According to Danzon et al.\textsuperscript{23}, each payer should adopt a decision rule about what is good value for money given their budget and, therefore, consistent use of a cost-per-quality-adjusted life-year threshold will ensure the maximum health gain for the budget. Several attempts have been made to establish such a threshold. The well-known example is the UK with a threshold of £30,000 for a QALY\textsuperscript{9}. Yet, in reality, interventions that at first sight appear to be cost-effective are not funded, while others with a seemingly very disadvantageous Incremental Cost-Effectiveness Ratio (ICER) are financed in full. The classic example of the first of these situations is the use of Viagra as a remedy for erectile dysfunction. Viagra was shown to have a cost-effectiveness of ±£5,000 per QALY, but there are very few countries where this drug is reimbursed by the health system. Stolk et al. refer to the perception by payers of this treatment as an “unnecessary luxury”, and not responding to a clear medical need. Having sex in advanced stages of life is perceived to be a personal choice, related more to lifestyle than to health problems. Viagra is, thus, considered to be a lifestyle drug, not eligible for public funding\textsuperscript{24}. In contrast, orphan drugs with an ICER of €150,000 per QALY or more are regularly reimbursed\textsuperscript{25}.

Stolk et al.\textsuperscript{26} have suggested that the willingness to pay for a QALY should formally depend on the severity of a condition for the patient. They refer to an “acceptable level of health” as a societal reference point. If people fall far beneath that acceptable level of health, they must be helped as a matter of priority and more should be paid for gaining a QALY. The opposite is also true. People with a health problem who are nonetheless above the acceptable level of health essentially have a “luxury” or “comfort” problem and, therefore, cannot necessarily rely on reimbursement of their treatment by the health system. Svensson et al.\textsuperscript{11} argued recently along the same lines from a Swedish perspective.

Following this way of thinking, in 2015, the Zorginstituut Nederland (ZIN = Dutch Health Care Institute) introduced a new and progressive approach, based on the premise that the limits of our societal willingness to pay for the gain of a QALY are not determined by a single value, but are dependent on the severity or the health burden of the health problem concerned. This is illustrated in Figure 1.\textsuperscript{27}

With severe conditions, policy-makers are more willing to pay to gain a QALY than with mild or moderately severe conditions. This, of course, means that the key question then becomes: how does one measure the health burden of a disease?

To solve this problem, the ZIN works with what is called the concept of “proportional shortfall”, which was first introduced by Stolk et al.\textsuperscript{26} as long ago as 2004. The basic idea is to calculate a ratio or proportion between the number of QALYs a patient would lose as a result of the condition, assuming it is not treated, and the normal number of QALYs that person would have enjoyed if he had never become ill.

An example will serve to clarify. Imagine that a patient is diagnosed with cancer at the age of 50. Let us further imagine that epidemiological research has shown that, if the cancer would not be treated, the patient could expect to experience an average of just five QALYs. Without the illness, he might expect to experience 25 QALYs. In other words, the patient would lose 20 of the 25 QALYs in his “reserve”. The proportional shortfall is, therefore, $(25 - 5)/25 = 20/25 = 80\%$. Real examples are provided in Lindemark et al.\textsuperscript{28}.

The greater the proportional shortfall of an illness, the more it is perceived as being “severe” and the more society should be willing to pay for the gain of QALYs. Recently, Reckers-Droog et al.\textsuperscript{29} suggested that further investigation into refining proportional shortfall – or exploration of another approach – appears warranted for operationalizing the equity-efficiency trade-off.

Another possibility to establish the severity of an illness is to conduct a multi-criteria decision analysis (MCDA). What should count for most when assessing the severity of a condition? The impact on quality-of-life? The likelihood of dying? Other factors? MCDA makes it possible to evaluate these different considerations by giving them a weighting, which, when taken together, determine the perceived level of severity. For instance, in an MCDA conducted in Belgium to compare medical need in different diseases, the researchers looked into the impact of the diseases on life expectancy and quality-of-life, on the age of patients, and the level of discomfort of the current treatment\textsuperscript{30}. Obviously, the drawback of MCDA is that the outcomes are determined by the selection of criteria. Recent initiatives such as the transparent value framework make use of this approach, although both disease and treatment characteristics are combined in that exercise\textsuperscript{31}. In the concept of modulated thresholds in function of disease severity, MCDA should contribute to better
quantify only that severity. For an overview of other MCDA exercises in this field, we refer to Wahlster et al.\textsuperscript{32}.

**Value informed, affordable prices**

The above model is not yet complete. Decision-makers typically also take into consideration the budget impact and affordability for the healthcare system. Indeed, even if a treatment is cost-effective, it does not mean automatically that it is affordable\textsuperscript{33}. This is undoubtedly a matter of opportunity cost. Putting too much money in one basket, i.e. one disease, takes away the opportunity to help other patients. A well-known recent example are the second generation direct anti-viral therapies for Hepatitis C: although very effective and even cost effective, their impact on medicines budgets in several jurisdictions would have been huge if all eligible patients were treated\textsuperscript{34}. Budget impact analyses are, therefore, required to assess the extent to which the healthcare system can afford to pay for the innovation. In this scenario, the possible offsets elsewhere in the system are to be taken into account as well\textsuperscript{35}.

Towe and Mauskopf\textsuperscript{36} discuss several ways to account for budget impact in decisions on pricing and reimbursement. One of these is to adjust the cost-effectiveness threshold in function of the budget impact. A higher budget impact requires a lower threshold and a lower budget impact can permit to work with an increased threshold. Applying this, and in combination with the above, this means that societal thresholds for willingness to pay for health gains need to be modulated depending on the disease burden as well as on the budget impact of the innovative medicine. Hence, for a treatment in an area with a high burden, and with a low budget impact, the societal willingness to pay for additional health outcomes should be higher\textsuperscript{37,38}. The opposite is true for a treatment in a disease with low burden and a high budget impact. Hence, when healthcare payers communicate explicitly about the societal thresholds within a value based pricing logic, and how they are modulated in function of disease burden and budget impact, it should be possible to reward value and at the same time account for affordability. This approach can be called “value informed, affordable pricing” (“VIA pricing”) and may become a practical approach to achieve pricing and reimbursement levels in line with societal values and preferences.

Figure 1 depicts this concept. We can again see the threshold line that was drawn in Figure 1, but now a number of additional lines have been added to reflect budgetary implications.

When the impact of an intervention on the budget is low or very low, as is the case with ultra-rare conditions, the threshold value can be increased. In 2017, for example, the British National Health Service announced that it was willing to set a threshold value of £300,000 per QALY for “exceptional” cases of this kind. But the same effect also works in the opposite direction: interventions with a high or very high budget impact can lead to the threshold being lowered. This implies a need to rely on the experiences of the past to determine precisely what constitutes “high” or “low” budget impact.

As an example, a new intervention for the treatment of a disease with a moderate health burden costs 35,000 euros per QALY. At first sight, this seems to be acceptable: it is well under the “standard” or average threshold value of 50,000 euros. However, if the budget impact of the intervention is high, this brings the threshold value down to just say 25,000 euros per QALY (figure is illustrative). This means that the intervention is not affordable, unless its price can be reduced. In cases of high budget impact, the company offering the new medicine is more likely to be willing to reduce the price, based on the principle that their turnover will remain high and that it is better to have a large market at a reduced price than no market at all.

The exact order of magnitude of the different thresholds could be determined by a trade-off exercise among decision-makers between cost per QALY, disease severity, and budget impact. Again, MCDA that can contribute to better understand the relative weight of these metrics are recommended to make progress in this field. For an extensive overview of the possibilities of MCDA with this regard I refer to Phelps.
et al.39. Another field of research is the conduct of regression analyses based on observed reimbursement decisions. A good example of the latter is the study conducted by Charakopou et al.40 in 2015 in Scotland, where it was found that the Odds ratio for reimbursement in case of an ICER below £30,000 per QALY was 2.96 (1.64–5.36), whereas the Odds ratio for reimbursement in case of a Budget impact in year 5 below £500,000 was 1.46 (0.94–2.26). Finetuning the methods of such exercises is increasingly important in the years ahead. Of course, specific characteristics of each country, such as ability to pay, epidemiological data, and cultural and societal values play a prominent role here.

In conclusion, we could turn value based pricing into value informed, affordable pricing by explicitly modulating thresholds of societal willingness to pay, thereby accounting for disease severity and budget impact. A research agenda for better estimating disease severity and quantifying the trade-off between cost-effectiveness and budget impact is required.

This if of course just one part of a bigger picture that should also investigate how to deal with evidence gaps at the time of submission, contracting between pharma and (multiple) countries and making the switch from paying for a product towards paying for a service, the latter stipulated by the expert panel on investing in healthcare8.

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